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Division of
Computer Research
and Technology

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

1988 Annual Report

Division of Computer Research and Technology

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
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Division of Computer Research and Technology
National Institutes of Health
Bethesda, Maryland 20892

Innovative application of computers plays a central and expanding role in support of the conduct and management of the NIH biomedical research programs. A large majority of the scientists and administrators are critically dependent on a daily interaction with one or more computer systems of their choice or assignment. An indirect but still an insightful view of the increasing magnitude of NIH computing can be gained by reflection on some "big number" statistics included in this year's report:

- The new Personal Computing Branch sends its technical newsletter to 5500 PC users at NIH and teaches courses for some 2300 students.
- The long established Computer Center Branch sends its technical newsletter to 18,000 users throughout NIH and other government agencies. It taught another 2300 students with interactive on-line courses as well as classroom sessions.
- The Data Management Branch performs extensive work on the NIH Administrative Data Base System, which serves the entire NIH campus and handles some 75,000 transactions on a typical day.
- The Laboratory of Statistical and Mathematical Methodology reports almost 90,000 monthly accesses to the math/stat packages it supports.

However, the numbers tend to obscure the fact that science and progress have their origins in the labor of the individual scientist on one research project, or the focus of the clinician on one patient, or the effort of the computer specialist to design one new or improved system.

It is the work of such individuals, often collaborating in small groups, that appears in the individual project reports from the DCRT laboratories. Together they cover a remarkable range of mathematics, engineering and natural science and a wide range of computer types and information processing disciplines.

Some of those individual projects in which scientists and computer specialists are involved include:

- Collaborations conducted with scientists in the National Institute of Neurological Disorders and Stroke and the Division of Research Services to noninvasively localized epileptic discharge sources in the brain. This is achieved using neuromagnetic recording in conjunction with conventional electroencephalogram (EEG) recording. This project involves the development of computer techniques for automating and enhancing the procedure for locating brain discharges in epileptics. In the coming year, findings will be enhanced by the integration of CT and MRI scans to provide three-dimensional displays of the head so that epileptic sources can be viewed anatomically.
- Providing software, hardware and scientific expertise to NIH scientists for image processing—including computer reconstruction of electron microscopy to better understand specimen structure. Few laboratories have the capability for image processing and image reconstruction available at NIH. The techniques are especially powerful when applied to two-dimensional crystalline structures. Processing is also proceeding on three-dimensional images as necessary software is acquired and developed.
- Studies with the National Institute of Diabetes and Digestive and Kidney Diseases and the Division of Resources Services on the diagnostic and therapeutic uses of laser light beams. Studies have shown that by using specially designed computer-based enumerations, certain information can be obtained by the way light diffuses when it is directed through tissue. By deriving the depths that light travels, scientists can, among other things, measure microvascular blood flow.

- Mathematical modeling of the cellular kinetics of the immune system, including interaction of T-lymphocytes, B-lymphocytes, macrophages and cytokins. By using a simulation that can examine a retrovirus-like infection, scientists hope to better understand how AIDS cripples the immune system. These models may also predict how the immune system will respond to therapeutic interventions and vaccines.

Efforts have also continued this year on three closely related networking projects, The DCRT Local Area Network project, the NIH Campus Area Network project and the Advanced Laboratory Workstation project. The DCRT Local Area Network has now been operating for four years, supporting workstations in Buildings 12, 12A and 12B. It has been widely used for daily production use, particularly the electronic mail and printing services it supports. This has been a valuable paradigm for research and development of NIH's Campus Area Network and Advanced Laboratory Workstation projects.

The NIH Campus Area Network Backbone, which will connect 32 buildings at NIH is progressing with work estimated to be completed in the first quarter of FY91. Local Area Networks will connect to the campus backbone through network interface units. The Advanced Laboratory Workstation project is exploring the uses of a network of 32-bit workstations employing the UNIX operating system as a means of providing the systems integration required to connect functionally a substantial number of laboratory-needed computers. This would allow computer software to run on a range of computer equipment for such endeavors as network communication, mathematical computing and equipment monitoring.

These and other efforts will continue to proceed in coming years to facilitate the use of computers to advance biomedical science in its full range of functions from basic research to administrative support.

Arnold W. Pratt

Arnold W. Pratt, M.D.
Director, DCRT

The Division of Computer Research and Technology (DCRT) has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH. DCRT serves as a scientific and technological resource for other parts of the Public Health Service, and for other Federal organizations with biomedical and statistical computing needs.

DCRT programs focus on three primary activities: conducting research, developing computer systems and providing computer facilities.

The **Office of the Director** provides overall program direction for DCRT, and serves as a central NIH focus for automated data processing policy. In addition, the Office sponsors research and development work in molecular and cellular graphics.

The **Personal Computing Branch** provides guidance and support to scientists and administrators throughout NIH in the effective use of personal workstations, local area networks and associated automation technology. PCB works closely with other DCRT labs and branches to monitor these rapidly changing technologies with a view toward the technical requirements of the user community so that these needs are accommodated in the development and support provided by DCRT.

The **Computer Center Branch** designs, implements and operates the NIH Computer Center and provides assistance, training and technical communications to the nearly 17,000 users.

The **Data Management Branch** serves as a central systems analysis, design and programming resource for data processing projects relating to scientific, technical, management and administrative data.

The **Laboratory of Applied Studies** relates mathematics, statistics, and computer sciences to such biomedical problems as ECG analysis, evaluation of physiological systems in health and disease, and estimation problems in laboratory medicine.

The **Laboratory of Statistical and Mathematical Methodology** provides statistical and mathematical help in the computer analysis of biomedical data and offers statistical and mathematical packages for users.

The **Physical Sciences Laboratory** conducts research in mathematical theory and practical instrumentation to explain biological phenomena in terms of chemistry and physics at the subcellular molecular levels.

The **Computer Systems Laboratory** provides consultation and collaboration in the design and implementation of specialized computer systems for laboratory and clinical applications.

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Office of the Director

Arnold W. Pratt, M.D., Director

The Office of the Director provides overall program and management direction for DCRT. The Director, Deputy Director, Assistant Director and Executive Officer work together as the immediate Office of the Director.

Two other offices supplement the work of the DCRT laboratories and branches:

The **Office of Scientific and Technical Communication** (OSTC) serves as central source of information about DCRT activities and about computing and related disciplines. It includes the DCRT Information Office and the DCRT Library.

The **Office of Administrative Management** (OAM) provides administrative and managerial support for the work of DCRT. OAM includes the Administrative, Personnel, Financial Management and Project Control Offices.

Also within the Office of the Director is the **Equal Employment Opportunity Office (EEO)**, which manages a full EEO program for the Division. The office serves as the focal point and advisory for all activities relating to the equal employment opportunities of DCRT employees and applicants. The EEO Officer maintains a close working relationship with the NIH Division of Equal Opportunity and other components concerned with minority and women's issues. The Office of the Director also has a molecular and cellular graphics research component that applies computing technology to biomedical research, to solve problems in macromolecular structure representation and modeling for collaborating NIH scientists and visitors.

Molecular Graphics and Simulation

For two decades DCRT has pioneered the use of new computing technology to enable biomedical scientists to visualize and explore the structure of important biological macromolecules.

In the early years Richard J. Feldmann developed and applied methods to create and rotate accurate diagrammatic three dimensional molecular structures. He expanded this to stereoscopic views and produced a monumental atlas of enzymes and other proteins.

In the middle period he and Thomas K Porter expanded on advances in computer graphics to create a new generation of stereo color pictures that emphasized the salient surface atomic properties important in interactions of proteins, nucleic acids and other macromolecules.

Early in the 1980's Feldmann conceived and constructed a molecular graphics laboratory that networked a variety of computing and graphic display devices to coordinate the strengths of each. This allowed up-grades of the components in a period when major improvements in the technology began to appear with ever increasing frequency. Later Bernard R. Brooks used the power of a pipelined vector processor in the network to create a pre-eminent facility for molecular dynamics simulations.

From the beginning the work has moved steadily from display of known biomolecular structures to the explication of modified structures to the prediction of new and hypothetical structures, from basic chemical and physical theory. The group has attracted scientific collaborators working both in the development of methods and in the application to specific biomedical goals such as vaccine development.

Research Projects

Computerization of the Grant Application and Review Process

Richard J. Feldmann

with J. Mathis (DRG)

The grant application and review process in the Division of Research Grants was partially computerized about 20 years ago by collaboration between DRG and DCRT. Since then the revolution in molecular biology occurred. The number of study sections more than doubled and the number of applications more than tripled.

The project is designed to determine if a computer can be used to assign incoming grant applications to study sections. After a consideration of complicated schemes using artificial intelligence techniques, it was determined that a simple table relating the 93 sections to 103 properties would provide an adequate method for making an assignment. The properties which apply to an application are selected from lists of diseases, disciplines, organs, test creatures and molecules. We used the prototype program to demonstrate the possibility of computer assisted application assignment by bringing workstations into the DRG. Later Dr. Mathis rewrote the program in Dbase III to consolidate our understanding of the problem and make it faster. The program is now in routine use.

After completing the prototype of the assignment program, an analysis was made of the flow of information in DRG as grants applications are received and reviewed. A month of programming produced a toy program called R01 after the major type of investigator initiated grant application. After a month the program was taken from toy to prototype and sent out to approximately 100 scientists at universities and medical schools. The first program was for IBM personal computers and their clones. Another month's work produced a program for the Macintosh personal computer from Apple. The response from this experiment was strong enough that DRG is planning a production version of the program for implementation of a completely electronic grant application and review process.

When the implementation process is complete, scientists can write their applications using their personal computers and send the floppy disk to DRG as the application. The floppy disk will be copied and sent to the reviewers, who using the same program will write their review and return the review either on the floppy disk or over BITNET. When the study section meets, a complete review report will be available and the production of the pink sheets will be much faster. The applicant will receive the pink sheets either on a floppy disk or by BITNET. Because all the information is computerized the review process has been shortened from 9 to 11 months to perhaps 4 to 6 months.

Dr. Mathis is now engaged in completely computerizing the routine work of the executive secretaries by using PC's and the Dbase III language.

In one year, this project has gone from an idea to a tentative solution, to a toy program, to a prototype program, to a production program, and in doing so completely transformed the information relationship between scientists and NIH.

Harmonic and Langevin Analysis of Large Systems

Bernard R. Brooks, Ph.D. and *Richard J. Loncharich, Ph.D.*

with: R.M. Venable (FDA); R.W. Pastor (FDA); M. Karplus (Harvard).

In this ongoing project, the use of harmonic analysis of large systems is used in a variety of ways to provide a better understanding of a protein and RNA systems. This work has involved performing many different types of harmonic analysis methods to the bovine pancreatic trypsin inhibitor as a trial system. Both harmonic and quasiharmonic analysis calculations have been carried out in several different bases. These results are currently being analyzed. Further work involving the Langevin mode analysis of this trial system and other systems is planned. From this work, we hope to: reproduce neutron spectral (time of flight) data; better characterize friction and solvent damping; find stress points in macromolecules; and explain (or predict) some site mutation data.

Development of New Theoretical Methods for Studying Macromolecules

Bernard R. Brooks, Ph.D. and *Richard J. Loncharich, Ph.D.*

with: B.K. Lee (DCRT/OD); R.M. Venable (FDA); R.W. Pastor (FDA).

One of the most interesting and important areas of ongoing research is new methods development. This work involves the development and characterization of new and untried techniques. Examples are: intelligent methods for processing conformational searching data; algorithms for performing Langevin normal mode analysis on macromolecules; DCRT developed new methods for performing free energy perturbation calculation; methods for treating solvent implicitly to provide for hydrophobic effects without the explicit inclusion of many water molecules; methods to allow a better use of NMR data in determining solution structures of macromolecules; and methods to rapidly compute the accessible volume and surface areas of a macromolecule. Most of these methods are being developed to provide future tools for applied projects in the coming years.

The Structure Determination of AIDS Glycoprotein Fragments

Bernard R. Brooks, Ph.D.

with: F.W. Carson (American University); R.M. Venable (FDA); R.W. Pastor (FDA).

This office is actively involved with the intramural effort to develop an antiviral agent for AIDS. Our initial work has focused on the three-dimensional structure determination of selected portions of the surface glycoproteins GP120 and GP41. The work performed to date proposes possible structures for the amphipathic segments of the HIV-1 gp41 envelope protein. This work may have implications for current vaccine development efforts. This work also suggests a possible mechanism for cytopathic effects of the gp120-gp41 complex. Further experimental data is still to come from NMR or from X-ray crystallography to support our efforts in designing an antiviral agent. In the interim, we will continue to look at protein fragments and trial systems to improve and calibrate methods.

The Use of Molecular Dynamics for Conformational Exploration and Structure Determination

Bernard R. Brooks, Ph.D. and *Jai-Lin Syi, Ph.D.*

Basic research projects are designed to provide a better understanding of biochemical systems and to find better ways to use existing methods. An example is the use of molecular dynamics for conformational searching. This approach is being extended to attack the protein folding problem from the small system end using the "brute force" approach. As computers become less expensive, this type of approach may provide better results than "intelligent" approaches, though a combined approach is a long range goal of our development efforts.

In addition to the basic projects which emphasize method development, these methods are now being applied to several projects of biomedical interest.

Theoretical Study of Polycyclic Aromatic Hydro-carbon-diol-epoxide-DNA Adducts

Bernard R. Brooks, Ph.D.

with: A. Weston (NCI); C.C. Harris (NCI).

In this ongoing study, the binding of diol-epoxides to DNA is studied. This project is approached by the modelling and simulation of carcinogenic aromatic hydrocarbon-diol-epoxide binding to DNA. The two main questions that this work attempts to answer are:

1) Can the wide difference in carcinogenic activity of similar adducts be explained from a theoretical study?

2) Can the cross-reactivity between adducts and antibodies grown against different adducts be explained?

The results of this work indicate a strong correlation between carcinogenic activity and orientation of the hydrocarbon in the minor groove of the DNA. This work also provides a possible explanation to observed cross reactivity data of antibodies grown against one adduct and DNA bound to different adducts. That explanation is that the antibodies recognize the distortion of the DNA backbone rather than the adduct itself and that structures that cause similar phosphate group movements have high cross-reactivities. This study also suggests a strong DNA sequence dependence for carcinogenic activity of polycyclic aromatic hydrocarbon-diol-epoxides.

Theoretical Study of beta-Lactam Antibiotics

Richard J. Loncharich, Ph.D. and *Bernard R. Brooks, Ph.D.*

The GAUSSIAN 86 series of programs will be used to carry out ab initio quantam mechanical calculations to model nucleophilic additions to beta-lactam antibiotics. There are plans to investigate the nucleophilic addition of hydroxide ion to the beta-lactam as a function of the O(hydroxyl)----C(carbonyl) reaction coordinate. The attack from both the alpha and beta faces will be considered to understand the steric and electronic requirements for stereoselective addition. Further aspects of the electronic nature of nucleophilic addition to the beta-lactam can be studied by substituting an amine (donating) group or a formyl (withdrawing) group at the carbon atom adjacent to the carbonyl. Placing substitutents on the lactam ring will indicate the polarization changes that occur as nucleophilic addition proceeds. There are also plans to study the binding of beta-lactams using a molecular dynamics approach for simulating chemical reactions.

GEMM, a Program for Molecular Simulations and Molecular Graphics

Bernard R. Brooks, Ph.D. and *Jai-lin Syi, Ph.D.*

Although the GEMM program has been running at full speed on the Star Technologies ST-100 for more than two years, there are several capabilities that have been added within the last year. These new features include the incorporation of periodic boundary conditions so that systems in a water box or lipid bilayer may be studied. Another feature recently studied is the ability to perform Langevin dynamics, so that systems can be coupled to heat a bath. The ability to carry out free energy perturbation calculations has also been added recently which allows these methods for binding calculations and for future drug design work. Another area of on-going development is the option to use lookup tables for both non-bond energies and for constraint energy terms such as a solvent boundary energy term. Other features and options are routinely added as needed to aid in execution of current projects. Currently the GEMM program is the largest application program ever written for the Star Technologies array processors.

The Graphics portion of GEMM has been ported to the new Stellar GS-1000 graphics superworkstations. Within the next year, the graphics and computer portions of GEMM will become tightly coupled.

A Two Gigaflop Computer for Macromolecular Simulations

Bernard R. Brooks, Ph.D.

We are currently in the design phase of a two year project that will result in the realization of a computer that will outperform today's supercomputers (Cray X/MP) by a factor of 20 to 30. This machine will be designed with special purpose integrated circuit chips that are being designed particularly for this project. It is intended that the total sale price of each of these machines will be about $150,000 each, resulting in a very high cost performance ratio which will be about 100 times better than any existing hardware. This machine should have a major impact on how molecular dynamics simulations are performed throughout the world. The project will be carried out through a cooperative research and development agreement with a computer manufacturer.

The Effects of Long Range Cutoffs on Protein Dynamics

Richard J. Loncharich, Ph.D. and *Bernard R. Brooks, Ph.D.*

Another basic research project is the study of the effects of long range cutoffs in protein simulations. To explore the effects of long range truncation on the molecular dynamics of proteins, a series of simulations on carboxymyoglobin are being performed. In this study we are systematically varying the distance and method for long range truncation. The two main questions which have been addressed are:

1) What is the best functional form for truncating long range forces?

2) What is the best distance to effect truncation?

Several additional questions have been addressed such as:

3) What is the effect of a short switching function?

4) What is the relationship between a constant dielectric and a distance dependent dielectric for pseudo-vacuum simulations?

5) What is the effect of increasing the dielectric constant?

This work will allow better protein simulations to be carried out by minimizing the effects of electrostatic truncation.

Office of Scientific and Technical Communications

William C. Mohler, M.D., Chief

The DCRT Office of Scientific and Technical Communications (OSTC), under the direction of the Deputy Director, DCRT, includes five people in:

- the **DCRT Information Office**, which is responsible for a comprehensive information program directed toward a variety of audiences within and outside NIH. The program is addressed to those whose needs and attitudes have important bearing upon what DCRT strives to accomplish; and
- the **DCRT Library**, which maintains a special collection in computer science, mathematics and statistics, along with computer applications in biomedical sciences, engineering, information science and management. Its information resources and services support DCRT as well as other parts of NIH.

DCRT Information Office

Colleen Henrichsen, Chief

Despite the departure of key staff members this year—and as a result, three different information officers—the Information Office manages to keep up with business as usual as well as to arrange several events with NIH-wide impact.

For the final NIH Centennial event, the Office assisted the NIH Employee Committee with Employee Recognition Day, by preparing the site maps, program and signage, and working on general site arrangements.

This year the office handled over 1000 requests for information and distributed over 10,000 publications on DCRT programs. It dealt with reporters and writers from a variety of media, including: ABC's "Health Show," Channel 5, *Federal Computer Week, Computer World, Labmedica, Datamation, Federal Times, Washington Technology,* PBS's "Nova," Time-Life books, and William Brown publishers.

Several groups received briefings and tours, among them visitors from China, and from other parts of NIH: NHLBI, NICHD, the DRR Minority High School Research Apprentice Program, and the NIH Executive Secretariat.

To provide our various publics with current information about DCRT programs, the office produced new editions of *Computing Resources* and the *DCRT Annual Report.*

Computerized typesetting was used for the seventh year to produce camera-ready copy for both documents, this time by two different input modes, one on 9-track magnetic tape, and the other on floppy disk, a successful first try. Our publications were recognized by outside organizations, with one award from Larami Communications and another from the Society for Technical Communication.

We contributed to other NIH publications: the *Report of International Activities, Research Advances, NIH Almanac, NIH Information Index, NIH Biotechnology Report, NIH Scientific Directory–Annual Bibliography, NIH Publications List,* and NIH's new recruiting brochure. In addition, we reviewed and edited a draft brochure for the NIH User Resource Center.

The office was again involved in creating presentations for the DCRT Director, for his annual research plan and for his appearances before various groups.

There were several PC-related activities, from upgrading to the PS/2 models, adding a laser printer, and converting the file of DCRT scientific papers to a SCIMATE data base, to learning the Zenographic software for presentation graphics.

The office suffered a dual loss with the relocation of two public affairs specialists—Patricia Miller to Battle Creek, Michigan and Joan Ackerman to Richmond, Virginia.

During what became the most active part of the year, DCRT Computer Specialist Margaret A. Douglas filled the void for more than two months. As acting information officer, she capably handled a mixture of activities, coordinating events for the Computers in Cardiology conference, hosting foreign visitors, arranging an all day "Image and Self Projection" video seminar, publicizing three seminars for the NIH-wide Image Processing Group, and installing two PS/2 model 60 computers in the Information Office. Also during this period, Douglas spearheaded the NIH Savings Bond Drive, supplementing the usual effort by arranging for Social Security representatives to be available to register employees' children.

In addition to handling the routine and the influx of new information activities, Douglas kept up with her major laboratory responsibilities and maintained active roles in the PWO Connectivity sessions, the NIH Women's Advisory Council (WAC) and the WAC Executive Board, and coordinated the annual DCRT employee picnic.

Colleen Henrichsen was appointed information officer in June, and Christine Pennella joined the staff as public affairs specialist in August, and during the last quarter both quickly became enmeshed in DCRT programs and events.

New staff members bring new talents and aspirations to the workplace. Such changes are even more obvious in a creative area like communications. The new public affairs specialists intend to apply their unique skills to develop and nurture interest about DCRT and its programs among its various audiences within and outside of NIH. Along with program leaders, the new staff will evaluate current communications needs of DCRT.

The staff will spend much of next year acquiring new skills in computing. They will meet other challenges as they arise, while assessing the Division's current and future communications needs; this planning and evaluation will continue into the next fiscal year.

DCRT Library

Ellen Chu, Chief

The DCRT Library maintains a collection in computer science, mathematics, statistics and computer applications in biomedical sciences, engineering, information science and management. Information resources and information retrieval and referral services support DCRT and other NIH projects and research. This year 89 new users from other parts of NIH registered to borrow from the collection.

The staff of three include the library director, a librarian, and a library technician. Ellen Chu, the library director, continued server administrator activities to support expansion of hardware and software installations on the LIB server. In addition to representing DCRT on the NIH Advisory Committee, she began a three year term in June on the Special Libraries Association Scholarship Committee, and a one year term as Finance Committee Chairperson of the Washington, D.C. SLA Chapter. This year, she served as an associate instructor in the PWO PC-DOS Advanced Topics class. Erica Lilly, the new librarian, joined the staff in January to conduct online reference searches, catalog new acquisitions, and help install the new library system. Anita Coherd, the library technician, handles acquisitions, serials control, and interlibrary loans.

Library automation of operations and use of national networks for cataloging, reference and interlibrary loans require constant training for staff to master new systems, databases, and to keep up to date with local hardware and software upgrades. Library staff training included areas such as network administration, specific databases, and Online Computer Library Center (OCLC) systems.

We installed ASSISTANT, the library application system that integrates online catalog, circulation, acquisitions, serials, and accounting operations. The catalog and circulation modules were initialized in January after acceptance of over 2500 catalog records of pre-1984 acquisitions processed by the vendor. Staff loaded the local database of catalog records covering 1984-1987. We closed the card catalog in April when we stopped filing new items. Users have been notified to consult the online catalog for new acquisitions. The library director installed Local Area Network (LAN) start volumes and two netstations for users to search the online public access catalog in the library and for staff circulation operations. In April, she created a DOWARE command (DO CATALOG) for access by DCRT staff via the LAN. The bar code labelling project of 6000 items in the collection began in late May with the arrival of a student summer employee.

ASSISTANT provides real-time and concurrent access in the DCRT network environment for library staff and other DCRT LAN participants. Library staff are now able to access and update the databases from workstations with no time lag. Users may search the online catalog in the library or from their offices. Circulation data entry for borrowers and items are now automatically entered by a bar code wand. We no longer log transactions by hand, followed by typing data entry. Status information is immediately available. We no longer need to consult batch reports and current manual logs to verify borrower and item status.

A new release of the system software in late summer extends functions and report capabilities. We hope upgrades will include report capabilities equal to the batch circulation system, designed and programmed for the library by the Data Management Branch in 1979. This system was gradually phased out with completion of the ASSISTANT catalog database.

ONLINE SEARCHES: This year, we added NEXIS to our online search services. DCRT staff requested numerous searches on federal databases, particularly the GSA Board of Contract Appeals. The Scientific and Technical Information Network (STN), which we added last year, continues to provide comprehensive author bibliographies with abstracts monitoring research in molecular graphics. The librarian also searches a variety of databases on DIALOG and National Library of Medicine systems for staff investigations. Search requests totalled 259, a 56 percent increase over the previous year.

CD ROM: As part of the collaborative project with the Personal Computing Branch, the library director installed a public user workstation to access BOOKS IN PRINT PLUS on CD ROM. We are now able to retrieve citations with incomplete data and with subject access. Users can also produce printed bibliographies by various selection criteria, such as subject or author. The disks are updated quarterly providing updates unavailable in the print editions. Although DNASTAR was also successfully installed, software complications necessitated postponement of this service.

DO NEWS LIB: The Library News Board is fully operational with news about services available in the Library or on the DCRT LAN. This year, the news board includes listings of on-approval book titles to be reviewed in the Library when they arrive. LIB NEWS is the mail group established for automatic distribution of these listings. The news board contains instructions on how to access the online catalog from workstations throughout the LAN.

DCRT LIBRARY NEWS: The DCRT MONTHLY ACQUISITIONS LIST was renamed DCRT LIBRARY NEWS with the addition of two regular features—a section on special journal issues received and spotlights describing online databases available for searching. We continue to distribute this monthly publication electronically via WYLBUR, DECMAIL, and ETHERMAIL, as well as paper copy.

The most comprehensive review of the journal and book collection was undertaken this year to remove obsolete and seldom used publications. Space constraints and initialization of the new integrated library system spurred efforts to make room for new materials.

At the beginning of the year, users reviewed title lists of candidate journal holdings to be removed from the collection. The early Association for Computing Machinery SIG (Special Interest Group) bulletins were transferred to the University of Washington ACM Depository. Other journals in print and microform were sent to Library of Congress or transferred to other NIH locations. In total, 1436 issues were removed from the collection, almost triple last year's weeding rate. Fifty-eight volumes of journals were converted to microform to save space.

In March, the Library Committee and library director reviewed two computer generated reports of candidate book titles: a circulation usage ranking report programmed by the Data Management Branch and a compilation of pre-1970 publications from our PC bibliographic database package. With the help of other volunteer members of DCRT staff, over 780 titles were screened prior to distribution of a title listing for final comments from other registered library users.

Next year, we will continue implementation of other modules of ASSISTANT, beginning with acquisitions. Installation of CD ROM systems on the network will depend on licensing terms which, in many situations, have not been established by CD publishers. Automation has introduced significant amounts of hardware into the library for both staff and users. We will work on improving our workspace to alleviate crowding and to improve work flow. We will also explore alternative document delivery options in view of our rigorous weeding programs to meet space limitations.

Office of Administrative Management

Marian Dawson, Chief

The Office of Administrative Management (OAM) serves DCRT by providing administrative support and resources allocation. Program planning and evaluation, and policy and legislative analysis functions also reside in OAM. The office is organized functionally into three sections: finance, personnel and administration.

The **Administrative Section** provides primary support for all administrative activities within the Division. The **Personnel Management Section** provides a full range of personnel services to the more than 300 Division employees. The **Financial Management Section** provides budget formulation and execution functions as well as managing the Project Accounting System (PAS), which provides detailed billing information to users of computer and programming services provided by the Division.

Fiscal Year Accomplishments

During the past year OAM staff remained heavily involved in the procurement for the replacement of the DEC-10, providing assistance to the project officer in the contracting activities. In addition, many hours of staff work were devoted to the development of an APR and associated requirements for the procurement of enhanced capabilities in the molecular graphics research area. New delegation of authority for ADP acquisition was received by the executive officer, and a new management mechanism was established to provide oversight of its use within DCRT.

The DCRT Personnel Operations Section prepared for the implementation of the new Employee Performance Management System Awards program. General orientation sessions were conducted for DCRT employees and supervisors, providing an overview of how this new program will benefit deserving employees.

DCRT recruitment activity continues at an active pace aided by several new "direct hire" authorities for computer specialists and a wide range of support positions. Once again DCRT made extensive use of the summer program, hiring more than 25 high school and college students in clerical, technical and professional fields.

Personnel Office staff participated in a career fair and contacted numerous technical schools and area colleges in an attempt to attract additional staff. The staff also initiated a new policy of conducting follow up interviews with new employees and attended numerous technical classes in an effort to provide even better service to DCRT employees.

The Administrative Office "fine-tuned" their past year's undertakings and current activities in the areas of reassigned duties, acquired staff and mandated procurement requirements of the NIH/PHS. Through personal observation and productive meetings with managerial and support staff of DCRT, methods for improvement in the communication and administrative arenas were developed, resulting in quarterly meetings with DCRT support staff and administrative personnel. A new tracking system for procurements was developed by members of the staff in order to assist Division managers in the tracking of pending requests.

In addition to the normal financial management functions of preparing routine budgetary documents and monitoring expenditures, the Budget Office prepared a complex request for additional positions and funds to support a major new initiative in intramural scientific computing during FY89 and 90.

A study of telecommunications charges and the billing process was undertaken. This resulted in correction of erroneous charges to DCRT of approximately $400,000.

Staff of the Project Control Office processed requests for new accounts and users of data processing activities, opening 125 new accounts and registering 2000 new users. The office also successfully completed its annual update of information on the over 3200 accounts and over 18,200 users currently in the Project Accounting System.

Future Plans/Trends

With an anticipated increase in the Division's budget in FY89 our new processes for tracking and reporting our financial resources will become especially important. We intend to continue to develop those systems and optimize their value to Division managers. The staff also intends to continue its education in the use of PC's and related software to accomplish their objectives. Plans are in place to bring Division staff up to date on major acquisition processes and to continue to assist them in a planning mode. A tracking system will be developed to assist with the new delegation of ADP acquisition authority recently given to BID Executive Officers.

PCB

Personal Computing Branch

David C. Songco, Chief

In FY88 the DCRT Personal Workstation Office evolved to the point where it had the resources and scope of activities to serve as a Branch and in September the Personal Computing Branch (PCB) was established by the Director, DCRT. This new Branch assumes all functions previously assigned to the Personal Workstation Office.

The PCB provides guidance and support to scientists and administrators throughout NIH in the effective use of personal workstations, local area networks and associated automation technology. PCB works closely with other DCRT labs and branches to monitor these rapidly changing technologies with a view toward the technical requirements of the user community so that these needs are accommodated in the development and support provided by DCRT.

The PCB staff has 22 full time employees consisting of computer specialists, engineers and training specialists. PCB was organized into four sections to better manage the continued growth. The Administrative Technology Section currently focuses on the IBM PC and compatible family of computers. Brian McLaughlin continues to lead the training program but now also heads the Scientific Technology Section. This section provides increased focus on support and guidance for biomedical research programs at NIH. This section also forms the basis for supporting the rapidly growing Apple Macintosh community at NIH.

The Communications Technology Section was established for support and guidance in all aspects of connectivity. The Consulting Service Section coordinates DCRT's participation in the NIH User Resource Center (URC). The PCB sponsors the NIH User Resource Center in collaboration with the Division of Personnel Management and the Division of Management Policy. The URC is used for hands-on training, user consulting, self study, user evaluation of hardware and software and as a source of technical literature. In FY88 in collaboration with the NIH Training Center we have completed plans and purchased equipment to open a new classroom by early FY89. This classroom will be used for Macintosh and Local Area Network (LAN) user training as well as for IBM PC training.

The centralized support provided by the PCB is enhanced by the PC Lead User Program. This program consists of over 200 BID nominated NIH employees who serve as the first line of support within the NIH personal computer user community. Lead users answer PC-related questions, provide training and disseminate PC-related information on behalf of the PCB. Lead users are also encouraged to participate in the PCB training program as associate instructors.

Advances In Technology

Personal computing continued to change rapidly with the profusion of PC's based on the IBM MicroChannel Architecture (MCA), the increased popularity of the Apple Macintosh technology, and the desire to connect computing at all levels. Evolving computer technology is challenging all of DCRT and users across NIH.

The PWO evaluated and announced support for several personal computers based on the new IBM MicroChannel Architecture. These PS/2 systems continued to evolve in FY88 with enhanced features and a general performance/cost reduction. Many hardware devices designed for the MCA were evaluated and then supported by the PWO. New PC applications as well as updated versions of currently supported software products were tested and evaluated by PWO staff, lead users and other specialists within DCRT. Early testing of the new Operating System/2 (OS/2) was begun to determine potential for use at NIH. Versions of currently supported software that are designed to be run under OS/2 should be available by early FY89. These application programs as well as communication and database software designed for the OS/2 environment show promise of both increased capability and an improved user interface. The PCB and other components of DCRT will be actively involved in selecting the best mix of products to provide a suitable computing base from which NIH users can operate.

Interest in presentation graphics was high in FY88 resulting in PWO support for several new software products. To meet the demands for varying types of data, devices such as image and text scanners were evaluated. Devices were evaluated that were designed for high resolution output, color and the ability to produce 35MM slides and overhead foils. The results of these evaluations were made available to the NIH community and support for several of these devices were announced.

Desktop publishing (DTP) increased in popularity in FY88. A document describing elements that make up typical DTP environments for various applications was published in FY88. In FY89 PCB plans to announce support for a variety of products that will form a common base for DTP functions.

Macintosh Support

In May, PWO began support for Macintosh personal computers by hiring two new specialists in Macintosh computers. Since then, the PWO has worked hard to quickly establish support for an estimated 500 Macintosh users at NIH.

Almost immediately, new staffers supporting Macintosh began accepting requests for advice and help through PWO's existing consulting system. PWO staff completed over 400 Macintosh consultations in FY88. We expect this number to substantially increase next year. As part of our Macintosh program the PWO also arranged and chaired the monthly meetings of the Biomedical Research Macintosh User's Group (BRMUG), the existing NIH Macintosh user-support group. Finally, we equipped the User Resource Center with Macintoshes and a LaserWriter to allow NIH users to evaluate Mac hardware and software.

Connectivity

This year the PWO began formal support for locally managed networks. The recommended process is similar to the existing PWO lead user program, but operates at the local level in a more structured manner via the use of designated server and network administrators. A pilot program was initiated to disseminate network information to the network administrators across campus who internet and exchange mail with DCRT. In addition, PWO has fully implemented handling network consulting from these administrators via its network 3Com supported Email system.

PWO also actively participated in the DCRT Connectivity Group. This group of DCRT technical staff was established in FY87 to help ensure a coordinated effort among the many projects underway involving communication between the different levels of computing at NIH. In April this group published a Connectivity Report containing descriptions of DCRT policies, services and technical guidance to assist NIH managers and planners in implementing effective communication between workstations and other computing devices.

Training

The PWO-coordinated microcomputer training program served a total of 2300 students enrolled in 115 sessions of 29 different courses. An average of 20 NIH employees a day received a full day of microcomputer classroom training. Vendors selected by the PWO and the NIH Training Center presented eight of the courses, while the remaining 21 courses were taught by PWO staff. Roughly half of the PWO/DCRT courses were administered by the DCRT training unit, for which there is no fee. There is a charge of $30 per day for courses administered by the NIH Training Center and taught by DCRT staff. (PWO Lead Users are exempted from charges.) This cooperative arrangement between the NIH Training Center and DCRT facilitated the addition of PWO courses and classrooms while effectively dealing with the substantial administrative overhead associated with running a diverse and extensive training program.

An important factor in the high quality of PWO training is the PWO Associate Instructor Program. More than 60 lead users have volunteered for this program, which they serve as assistant instructors for an average of four days a year. This allows for both a main instructor and two assistants for each hands-on class.

In addition to these NIH-wide courses, BIDs also made use of the vendors screened by the NIH Training Center and the PWO to provide specially targeted training.

Lead User Topic Sessions

Monthly Lead User Topic Sessions continued throughout FY88. These meetings are organized and co-chaired by a PWO staff person and a BID representative. Sessions consist of demonstrations, tutorials and discussions of computing topics relevant to lead users. Topics have ranged from graphics programs and local area networks to the use of DOS utility packages and mainframe connectivity. Attendance is voluntary and ranges from 30 to 90 lead users per session. Lead users also participated in PWO-sponsored working groups, designed to identify and explore relevant issues in specific areas of interest. The WordPerfect group was the most active in FY88.

Consulting and Guidance

With the proliferation of the IBM PS/2 family and the rapid rise in popularity of the Macintosh, both the number and variety of workstations in use at NIH increased this year. This coupled with the heavy demand for consulting on connectivity topics resulted in 700 consults per month by the end of FY88. Guidance was provided in a wide range of areas including wordprocessing, database management, printer selection, forms generation as well as questions regarding the supported architectures for workstations and local area networks. The number of inquiries for guidance in the selection and use of local area network technology, Macintosh computers, graphics and desk top publishing elevated significantly. Overall the

PWO consulting service answered over 8000 requests for assistance from NIH PC users this year.

PWO Publications

Six issues of "PWO Newsbrief"—the PWO's technical newsletter for NIH microcomputer users—were published and distributed to 5500 PC users at NIH this year. Over 300 Macintosh users were added to the circulation of Newsbrief, which now includes articles and columns on a variety of Macintosh topics. An updated "PWO Product Information Guide", describing PWO-supported hardware and software and the levels of support available from the PWO is scheduled for release early in FY89. The PWO staff also developed and distributed a number of technical notes to the NIH user community.

PIF and PUF Diskettes Provide Useful Utilities and Automatic Software Installation

The long awaited upgrade to the PWO Utility Disk was released in January 1988 in the form of two new diskettes: PWO Installation Files (PIF) and PWO Utility Files (PUF). In addition to installing DOS and certain PWO-supported application programs on new systems, these diskettes can be used to automatically bring anyone's hard-disk structure in line with PWO recommendations. The PIF diskette has already been used to successfully install DOS and other software on hundreds of PC's at NIH. The PUF diskette features a wide-ranging smorgasbord of public domain utility programs, written by DCRT staff and others. This wealth of disk- and DOS-related utilities also includes miscellaneous routines and procedures such as a set of Lotus 1-2-3 macros and a PWO-supported "shell" program.

The Future of Personal Computing At NIH

In a few short years the PWO has grown in size and capability to meet the challenge of the rapidly evolving personal computing technology. Next year as the Personal Computing Branch we hope to provide full Macintosh support as currently provided for the IBM PC community. Work will continue with other DCRT components to phase in the new OS/2 operating system. In FY89 we also expect to provide more specific guidance to those NIH groups planning and installing local area networks as experience with larger networks is gained and the products in this area mature. Most importantly PCB plans to increase its attention to scientific computing as new architectures emerge.

CCB

Computer Center Branch

Joseph D. Naughton, Chief

The Computer Center Branch designs, implements, operates and maintains the central NIH Computer Utility and its associated telecommunications facilities. Two interconnected multicomputer facilities designed around large-scale IBM and DEC mainframe computers make up the NIH Computer Utility, which provides computational services to support the dynamic and diverse requirements of NIH research investigators and administrators in the conduct and management of modern biomedical research.

The Utility provides interactive timesharing, database, graphics, batch processing and word processing services to approximately 18,000 authorized users at NIH and in 26 agencies throughout the federal government as a Federal Data Processing Center (FDPC). All work is processed on a fee-for-service, full cost-recovery basis.

The IBM facility, valued at over $65 million, is made up of six IBM 3090 processors (three with Vector Facilities) containing a total of over 384 million bytes of directly addressable memory. The peripheral complex includes 624 online disk drives with a total data storage capacity of over 750 billion bytes; 108 cartridge tape drives with a transfer rate of 3MB/second; 20 reel tape drives with a transfer rate of 780 KB/second, and four with a transfer rate of 200KB/second; seven 18,000 lines-per-minute and five 1100 lines-per-minute page printers; two 1000 card-per-minute card reader/punches; and 13 telecommunications controllers supporting a teleprocessing network of over 1500 lines of various bandwidths connected to 301 remote job entry (RJE) computers and 10,000 conversational CRT and/or hardcopy interactive terminals located throughout the world.

The DECsystem-10 facility is designed around three KL10 and one KS10 processors with three million words of main memory; 12 554 megabyte disk drives and 19 197 megabyte disk drives; seven 780KB/second and three 200KB/second tape drives; and 11 communications processors capable of supporting over 75 simultaneous timesharing users.

The two facilities are linked together by high-speed telecommunications lines to facilitate the exchange of data, mail and programs. Ancillary equipment supporting both facilities includes two computer output microfiche units and film processors, two four-color high resolution plotters, and other miscellaneous devices. Services of the Utility are available worldwide through the TYMNET and BITNET international data communications networks as well as through the Federal Telecommunications Service (FTS), commercial switched telephone services or over dedicated (hardwired) communication lines.

The NIH Computer Utility operates 24 hours each day, seven days a week; processes over 18,000 batch jobs, 11,000 interactive sessions and 75,000 database transactions daily. Over 90 percent of all interactive commands are executed with subsecond response time, and six service classes for batch jobs guarantee maximum turnaround times of less than 30 minutes, one hour, two hours and overnight.

Applications are programmed in FORTRAN, COBOL, PL/1, BASIC, C, Assembly Language and SAIL using three interactive programming systems (TSO, WYLBUR and DECsystem-10 Timesharing). Database management services are provided through DB2, a general purpose open shop relational database system, and IMS, an interactive transaction processing system for complex administrative applications. A variety of statistical analysis, modeling, data management, and utility programs are available, as well as the TELL-A-GRAF, POSTER and OMNIGRAPH interactive graphics packages.

An in-house training program offers 40 specialized classroom lecture courses four times a year, while an interactive Assisted-By-Computer (ABC) training system permits users to develop expertise in the use of the utility in the privacy and convenience of their own work environment. An extensive array of technical documentation ranges from a comprehensive *Computer Center Users Guide*, which defines all available services, standards and procedures, to a technical newsletter, *INTERFACE*, which keeps users up-to-date on the current status of the utility and announces changes and upgrades as they occur.

A highly specialized staff of professional, technical and management personnel ensure smooth functioning of the NIH Computer Utility. Computer systems programmers and analysts develop and maintain operating systems software, provide technical consultation on program design and problem resolution, teach training courses and write technical documentation. Computer systems technicians and operations personnel operate and maintain the Computer Utility's hardware and telecommunications networks and provide support services. Systems design and management professionals develop long-term program goals and maintain the design integrity of the utility.

The Computer Center also conducts a number of research and development projects to increase the effectiveness of computers in the support of modern biomedical research.

Progress Toward the Future

The major focus of the Computer Center staff this year was continued work on fully competitive acquisitions for the complete replacement and upgrade of both the IBM System 3090 and the DECsystem-10 based facilities. When complete, those acquisitions will provide NIH the most modern and cost effective computational technology for both scientific research and management applications available in the marketplace for the next ten years. Following over three years of concentrated effort, contract awards for both systems are anticipated by the end of FY88.

The Request for Proposals (RFP) for the IBM System 3090 replacement specifications require a single prime contractor to provide and support a "Total System" computation capability for NIH for a period not to exceed 10 years. That is, NIH will acquire a fully integrated and operational set of compatible hardware, software and support services capable of solving existing and future computational problems of modern biomedical research and management. The proposed system and contract must provide maximum flexibility for the continual evaluation (i.e., modification, upgrade and/or replacement) of system components to improve operational or functional characteristics and to incorporate the use of new, more modern technology and methodology as they become available throughout the 10 year life of the contract. It is mandatory that the proposed system be fully compatible and functionally equivalent to the present system at the application programming and operating system command language level. All existing applications programs and JCL will continue to run without change. An extensive benchmark composed of actual NIH batch jobs and interactive sessions selected from the standard NIH Test Job Stream (TJS) was required to size the proposed system and to verify program compatibility with the present system.

Onsite hardware and software maintenance service as well as system engineering, management and support teams are also required. An appropriate complement of technical documentation and training courses, as well as a number of evaluated optional features are also required.

As the DECsystem-10 facility celebrates 15 years of scientific timesharing service to the NIH community, preparations are being made for introducing a replacement system. Since the DECsystem-10 architecture has been discontinued by the manufacturer, Digital Equipment Corporation, further upgrades of the present system are no longer possible.

After much discussion and review with the NIH scientific research community, the Computer Center determined that a completely new computer utilizing the UNIX operating system offered the greatest potential for effective long-term service as a scientific timesharing system. An RFP which emphasized specific technical requirements such as the UNIX operating system, networking capability, programming support, maintenance, documentation, etc., that are particularly suitable for basic research applications was developed and issued. Certain qualities associated with the DECsystem-10 but often not associated with UNIX systems were incorporated in the RFP as subjective evaluation criteria to permit selection of the system with the greatest value rather than the lowest cost. Examples include system management tools, batch processing, quality of support services, comprehensiveness of documentation and training, and experience in similar installations. The resulting contract will provide maximum flexibility to respond rapidly to both changing user requirements and technology as they evolve throughout the five year life of the contract.

New Facilities Offer Paperless Communications

A new era of computing began at the NIH Computer Center this year as new, easy-to-use, extremely flexible computing facilities were developed for researchers, clerks, managers and administrators. No longer exclusively devoted to the design of tools for professional computer programmers, the NIH Computer Center now provides "services for people."

The most important new service introduced this year addresses the time-consuming and inefficient communications process. Typically, countless hours are spent establishing telephone contact, writing and distributing memos, circulating reports and research papers for comment and filing letters and documents—at the same time generating an incredible volume of paper. No longer is this the case at NIH, with the advent of a new ENTER MAIL facility designed to provide one of the most comprehensive electronic mail and communications processing capabilities available today. ENTER

MAIL allows mail, messages, documents and reports to be sent, read, printed, filed, forwarded and answered quickly and easily without paper.

In response to the popularity of the RECEIVE and MAIL commands available through WYLBUR, ENTER MAIL incorporates all of the features of older commands and offers powerful new facilities for handling incoming mail. Little or no computer expertise is needed to use the facility, which enables users to communicate with others on the NIH campus or throughout the world at electronic speeds, free of unnecessary paperwork and ringing telephones. ENTER MAIL represents a major step toward creating "the office of the future" at NIH.

Designed and written at the NIH Computer Center, ENTER MAIL is being constantly improved to meet the changing needs of NIH users. It incorporates a COMMENT command that allows users to suggest changes and improvements, and a number of such enhancements were incorporated during the past year.

BITNET, the international network of research and academic institutions that was originally introduced in 1986, enjoyed a surge in popularity in FY88, in part because its interface to ENTER MAIL facilitated the movement of electronic mail "around the world or across the hall." Several enhancements made BITNET communications more efficient and powerful and a number of training seminars were held to meet numerous requests for information and to address the burgeoning popularity of the network.

Use of BITNET at NIH increased to over 21,000 mail and file transfers per month, with no sign that the steady growth is abating. The BITNET network grew to include some 2500 nodes at over 900 educational and research institutions throughout the U.S., Canada, Mexico, Europe, the near East and Japan—and the number is still increasing. Gateways from BITNET provide access to other networks such as ARPANET, NSFNET, CSNET, SURANET, etc. Domestic communications were usually completed in less than a minute, with most transmissions to Europe or Asia taking no more than several minutes. Even under the worst conditions of heavy network traffic, intercontinental communications took only a few hours.

BITNET has not only reduced the frustrations of conventional forms of communication, it has radically altered the way biomedical research activities are conducted by enabling research scientists and educators to communicate instantaneously with colleagues world wide. For instance, international conferences have been announced to the worldwide research community via BITNET, coordinators have utilized the network to contact speakers and committee chairmen, prospective attendees have preregistered electronically rather than sending in a mailed response, and conference organizers then used the network to forward information on travel and accommodations to attendees.

Thus, BITNET simplified the process of arranging scientific conferences and significantly reduced the costs. Calls for papers have been handled in a similar manner, and collaborating authors have been able to distribute rough drafts to colleagues and receive comments back in just hours or days. Scientists and administrators utilized the network to exchange information with grants reviewers at distant locations. Together, BITNET and ENTER MAIL constitute a major step toward the electronic office of the future.

EXCHANGE, the NIH Computer Utility's professional bulletin board service, proved to be another popular means of paperless communications during the past year. A number of upgrades to the EXCHANGE were installed in FY88, including dated entries and automatic expiration dates for short-lived information. The enhancements made the EXCHANGE more powerful and functional, and reflected user comments and suggestions.

Data Migration System Conversion

A pioneer in the use of large public online DASD storage, the NIH Computer Center was one of the first computer installations to develop a system for automatically migrating inactive data to keep pace with increasing demand for data storage space. In October 1973, the Computer Center designed and implemented one of the first data migration systems which automatically copied data sets that were not being used to magnetic tape, freeing online disk space while keeping less frequently used data easily available. The system provided simple mechanisms for determining what data sets had been migrated and retrieving them as necessary. This was a forerunner of many of today's commercial data migration systems.

A new completely redesigned data migration system, using state-of-the-art software and hardware technology, was completed and made operational on the NIH Computer Utility in FY88, after months of rewriting, testing and debugging. Based on 3380 double density disks, 3480 cartridge tapes, and IBM's Hierarchical Storage Manager (HSM) software, the new system improves performance significantly, offers new data migration features and gives users more information about migrated and online data sets.

HSM provides basic data management functions which were tailored to meet the unique requirements of the NIH environment. The new data migration facility initially stores data sets in compressed form on 3380 disks where they can be quickly retrieved without operator intervention. After an additional period of inactivity, data sets are automatically written to tape, where they can be accessed, if needed. The new system allows users to display format characteristics, space attributes, names and volumes of both active data sets and those stored on Dedicated disk volumes and Managed Storage (MSS). A much requested "migrate on demand" feature is also provided by the new migration system.

Migrated data sets may be scratched from the migration index, and users can rename data sets in the migration index, making it possible to reassign data sets to other users without first retrieving them. The new data migration service also allows migration of Physical Sequential, Partitioned, Direct Access, VSAM, and RACF-protected data sets. With the old system, only non-RACF protected Physical Sequential data sets were eligible for migration.

DB2 Gets Better and More Popular

DB2, the effective and easy-to-learn relational database management system introduced in December 1985, proved so valuable for many users of the NIH Computer Utility that service hours were increased 155 percent in September 1988. Formerly available interactively only from 8:30 a.m. to 5 p.m. Monday through Friday, DB2 service was made available for interactive and batch access from 8:30 a.m. to 12 midnight, seven days a week.

This increase in service hours enabled DB2 users to make fuller use of the service while saving money, as all work processed after 5 p.m. EST Monday through Friday and all day on weekends is discounted by 60 percent. The extended hours of availability also made DB2 effective for a wider variety of applications, particularly in clinical settings where information must be available seven days a week.

The NIH Platelet Center used DB2 in FY88 to organize blood compatibility information from over 3000 donors. Histocompatibility (tissue) matching of patients with donors can now be completed in seconds, with the resulting information presented online at the user's terminal. Thus, DB2 has enabled the Platelet Center to reduce substantially the time needed to match patients with suitable platelet donors.

DB2 received several major enhancements to make the service even more efficient and useful this year. New releases of the DB2 family of products were installed to provide users with a full set of tools for date and time computation, conversion and reporting. Numerous improvements were made to the Structured Query Language (SQL) used with DB2, to both add new features and increase flexibility as well as to increase adherence to the ANS standard for the SQL language. SQL is rapidly becoming the most widely used database query language in the industry, and increased standardization proved advantageous to users as they built upon previous experience to develop new applications.

Other, more transparent, performance improvements reduced bottlenecks and improved the function of the optimizer, which determines the most efficient way to retrieve data requested in an SQL query. This improved performance for interactive sessions and batch jobs and reduced system resource requirements, thereby reducing the cost of DB2 services.

Rates Are Reduced and Refunds Offered

In keeping with long established tradition, the NIH Computer Center offered significant rate reductions to users of both the IBM System 370 and the DECsystem-10 in FY88. This marks 20 years of continuous rate reductions for users of the Computer Utility.

- The charge for TSO and DB2 CPU time was reduced 16.7 percent to $1.25 per CPU second.
- The cost of IMS, the Computer Utility's transaction-oriented database system, was cut when the 18 cents per transaction portion of the IMS billing algorithm was reduced to 17 cents.
- The rate for editing time in WYLBUR was reduced 4.2 percent to $1.15 per second of editing time.
- The cost per machine unit for batch jobs was reduced 3.3 percent, to 29 cents, guaranteeing batch costs that are among the lowest in the industry.
- Cost effectiveness of online disk storage has increased, when the rate for data stored on FILE, CNTL and TMP packs was cut 17.6 percent, to $.014 per track day.
- The cost of the Managed Storage System was reduced 12.5 percent to $.0035 per track day.

- The cost of private disks was reduced to a minimum charge of $2625 or $.00875 per track day.
- Rate reductions were not limited to the IBM System 370; users of the DECsystem-10 also received the following rate reductions:
- The cost of a machine unit on the DECsystem-10 was reduced by 9.8 percent to $.55 per machine unit.
- Data storage rates for the DECsystem-10 were cut 12.5 percent to $.056 per 100 blocks per day.

In spite of the rate reductions, the Computer Center's continual efforts to keep the cost of high-quality computing as low as possible resulted in significant cost savings during the first half of FY88. The resulting $3 million savings was shared by all users of the NIH Computer Utility in May when it was refunded based on the amount of use during the first part of FY88. The cost savings continued into the second half of FY88. Based on accumulated plus projected savings for the remainder of FY88, the users shared another $3.8 million in July. The total refund amounts to approximately 16.7 percent of the total charges billed through the end of July.

The savings resulted from a number of factors. The volume of work expanded, reducing the unit cost for all users. As technology itself improved, greater cost effectiveness was possible, and implementation of the latest hardware and software components further improved the price/performance ratio of the NIH Computer Utility. New operational procedures made more efficient use of system resources, and vendors reduced the price of some hardware and software products while improving the performance of others. These factors combined to enable the utility to provide the most advanced services available anywhere at the lowest possible cost.

New Products and Services

It became possible to process all classes of work during the prime (daylight) shift this year. The increasing power and flexibility of the latest hardware and software technology enabled the Computer Center to satisfy a long-standing user request to process Class C work during the day shift. Now, all job classes are available all of the time. The running of Class C jobs during the day gives users the opportunity to rerun jobs that failed the previous night, and the ability to better meet last minute demands that require Class C jobs.

The rapid growth in use of WYLBUR Command Procedures (CP's) has demonstrated the value of that technology. The Computer Center, recognizing the value of those tools, announced the ability to compile and save CP's for multiple use without the necessity of recompiling at each usage. The saved compiled CP's are invoked exactly the same way as their non-compiled versions and are faster and lower in cost to use. One user estimates an 80 percent savings in the cost of executing CP's used by dozens of his fellow workers.

Electronically controlled computer output storage boxes, installed at the NIH Computer Center in September, replaced the old open cabinets previously used to store computer output printed at the central site. The new locked boxes increased security for sensitive output as required by the Privacy Act, and enabled users to control access to their printed output. Similar in appearance to the storage lockers used at airports, the boxes are opened by a seven digit code punched into a keypad located in each bank of boxes.

New microfiche equipment was installed that provided clearer, easier to read images with less glare. The new equipment uses a reversal process that results in clear lettering on a dark opaque background. It is not nearly as susceptible to dust and other environmental or chemical variations and cannot be accidentally over-exposed.

A new map data file gave users the ability to draw a complete United States map using TELL-A-GRAF Version 6.0. Graphic outlines of the states can be used individually or in any combination, and the states can be colored or shaded in different ways, enlarged, or moved anywhere on a page.

The introduction of a "C" language compiler on the IBM 3090 System extended the power of the Central Facility by permitting the porting of programs written in that ubiquitous language across the full range of computing hardware—PC's to mainframes. The many scientific and data processing applications written in C can now use the full services of the mainframe environment.

A number of services and programs were retired in FY88. Technical progress in the automation of data collection made manual keying of data from documents obsolete; therefore, the Computer Center's Data Entry Service was closed after many years of dedicated service. Also discontinued was the Electronic Spread Sheet (ESS) software package. First introduced in 1985, ESS never became popular and had only four regular users during the past year. The Indexed Sequential Access Method (ISAM) was phased out during FY88 because of declining support from the vendor as the newer VSAM access method took its place. ISAM was officially retired in July 1988.

Documentation, Training and Assistance

The NIH Computer Center's documentation services took a giant step forward into the age of automation in FY88 with the installation of PUBWARE, a system that lets users request documentation interactively through WYLBUR. The new service, Publications and Software Services System, is accessed by simply typing the command ENTER PUBWARE in WYLBUR. The command may also be used to display abstracts of publications, list the most current version of a publication, renew or cancel subscriptions, and list the user's publications profile (e.g., titles sent automatically).

User reaction to the new ENTER PUBWARE facility was overwhelmingly positive, and dozens of favorable comments were received in the first few months PUBWARE was available. Already, over 3500 requests for documentation have been submitted through the ENTER PUBWARE command.

New documentation produced in FY88 included publications on ENTER MAIL, BITNET and DB2. The *Computer Center Users Guide* was updated six times and the *DECsystem-10 Timesharing Guide* once; there were nine new technical documents published and 16 revisions or updates. The Automatic Documentation Service was used by 6829 users and 146,854 copies of technical publications were sent to those users and to individual requesters. Seven issues of *INTERFACE*, the Computer Center's technical newsletter, were published and distributed to all users this year.

Providing high-quality training in creative ways is an ongoing activity of the NIH Computer Center Training Unit. This year 106 sessions of 39 different courses were offered in the formal classroom training program. Of the 1752 students who requested training, 1524, or 86 percent of them, were accepted into the formal training program.

Short, informal seminars on such topics as DB2, Vector Processing, Kermit, ENTER MAIL and BITNET proved very popular during the past year. All short courses of one to three hours were removed from the normal training program and offered as seminars. Whenever possible, a second session was scheduled as soon as a seminar became filled, and subsequent callers were given the new date and time.

Independent study courses were heavily utilized by those who could not take the formal training courses. The seven popular Assisted-By-Computer (ABC) courses provided educational options for many Computer Utility users. More than 850 users completed ABC courses this year, and approximately 11,000 interactive ABC sessions were held.

This year, Computer Center consultants handled 16,560 requests for customer assistance. Over 2000 Programmer Trouble Reports were researched and answered. Changes to improve the performance and reliability of the operating system required the implementation of 30 SYSGENS (software reconfigurations). Approximately 22,600 fixes, both preventive and corrective, were tested and applied to the system and 54 new releases of current software packages were installed.

Initiatives for the Coming Year

Work will continue in the coming year to tap the capabilities of personal computers (PC's) with the tremendous power of mainframes by developing hardware and software technologies to integrate Local Area Networks (LAN's) with the NIH Computer Utility. LAN's allow mini, micro and mainframe computers to communicate among themselves and to transfer mail, documents and files between computers on the same LAN.

The NIH Computer Center will assume a pioneering role in developing technologies to allow mail, file transfer and terminal access both within LAN's and across different LAN's. A broadband backbone network is being planned for the NIH campus to allow megabit per second transfer between LAN's on the NIH campus and the Computer Center mainframes. A wide range of computer technologies will be studied to assure that systems implemented for the mainframe computers will be compatible with the backbone network. Ultimately, LAN's on the NIH campus will be connected directly to the backbone network. This connection will replace the high speed telephone lines currently used. Off campus LAN's will utilize other state-of-the-art broadband teleprocessing technologies.

New avenues for applying computational techniques to the problems of biomedical research continue to be explored. The Computer Center moves into the future armed with new contracts that will enable it to continue providing the most modern computer facilities utilizing the latest in computational methodologies at the lowest possible cost, to its intrepid users. The staff of the Computer Center remains dedicated to these goals.

Data Management Branch

J. Emmett Ward, Chief

The Data Management Branch (DMB) provides advice and assistance to research investigators, program officials and administrators throughout NIH in planning for and obtaining computer data processing services. In this role the branch is a central NIH resource for systems analysis, design and programming. The Branch is also responsible for the development, maintenance and processing of the NIH Administrative Data Base and the Clinical Center's Clinical Information Utility. There are currently 47 permanent full-time employees whose disciplines include computer science, mathematics and statistics.

DMB staff members design and create computer-based data management systems that provide practical solutions to the unique mix of administrative, scientific and management data processing problems encountered at NIH. Each new computer system user is provided comprehensive training in all facilities and functions of any system developed by DMB. In addition DMB staff members teach courses about programming tools; provide advice on data management techniques to NIH programmers; serve as consultants to the NIH Bureaus/Institutes/Divisions (BID's) for obtaining and monitoring contracting services for computer systems development; and create and maintain general purpose, user-oriented programming tools to speed building and improve operation of applications systems.

DMB comprises four sections. The **Applied Systems Programming Section** (ASPS) and the **Scientific Applications Section** (SAS) provide general computer systems analysis and programming services for all of the BID's. The ASPS supports general data management, and the SAS handles those projects that require scientific data analysis.

The **Data Base Applications Section** develops and maintains the central administrative data base for NIH materiel and financial management. The **Clinical Support Section** develops and maintains the Clinical Information Utility as a data base for research and patient care in the Clinical Center.

Broad Involvement in the NIH Mission

The NIH Administrative Data Base (ADB) is an ongoing developmental project that uses online data base technology to support NIH-wide materiel and financial management. Systems that support the following functions have been developed to share the ADB in a fully integrated environment:

- Market Requisition
- Stock Requisition
- Central Procurement
- Delegated Procurement
- NIH Inventories, Central Stores, Self Service Stores, Clinical Center Pharmacy, Clinical Center Materiel Handling, Biomedical Engineering and Instrumentation Branch (BEIB) and Division of Engineering
- Services (DES)
- Receiving
- Accounts Payable
- Source Contracts
- Vendor and Vendor Credit
- NIH Cashier and Vendor Credit
- Service and Supply Fund Users and Services.

DMB has continued the conversion of service and supply fund activities to the ADB. During the past year, telecommunications and photography have been added. The Division of Engineering Services has also begun its pilot test and should be fully operational by the end of the fiscal year. Both graphics and transportation should also be implemented in early FY89.

The first rendition of travel management will include order entry, order change and advance processing for domestic travel. It is anticipated that these functions will be available in the ADB by the end of FY88.

A personal computer system for NIAID to support data collection and analysis for the AIDS vaccine trials was completed this year. Each test center was provided with its own software and data can be automatically transferred to NIH, combined with other test centers and analyzed on the mainframe. A contract was recently obtained to operate a data coordination center for the trials to support all software and documentation.

A fund analysis system was developed and implemented to track funding and spending by the standard management accounts structure, budget activity and the congressionally mandated mechanism concept. These data are updated nightly and made available on line to the BID's and central NIH Budget the following day. DMB is currently in the process of training interested NIH personnel and offices in the access and use of these data.

In the interest of automating various aspects of the preparation of the *NIH Scientific Directory-Annual Bibliography,* DMB has developed a computer system which significantly reduces the time necessary to achieve a final product while also providing edits to assure more error-free results.

To support the Office of the Director, NIH, DMB has developed a correspondence control system for the Executive Secretariat. This system keeps track of all correspondence received by the OD, records all referrals and provides followup on overdue responses. It also provides quick reference information on a multitude of data related to each correspondence. The current system runs locally on four PC's and is awaiting a file server. When the file server is available, the system will be converted to share a single data base on a local area network.

Future Plans

During FY89, DMB plans to complete its in-house conversion to multi-use personal computers which provide local processing, network processing and full access to all mainframe facilities. This conversion will reduce the need to duplicate terminals for dissimilar tasks, and will also save $75,000 per year in equipment rental costs.

A system to support medical records processing in the Clinical Center will be converted to personal computers during the next fiscal year. This system will serve as a reasonable prototype for local data collection and central maintenance of mainframe data prior to its full conversion to a personal computer shared data base system. The major long-term test for this system will be to determine the feasibility of maintaining a relatively high-volume transaction processor with a quick reference facility on a shared data base in the PC environment.

The Fogarty International Center (FIC), OD, NIH and the Division of Financial Management (DFM) have requested the development of a computer system to support all processing of data in the visiting scientist program. A data base system is needed which will permit point of origin entry, sharing of data among preparation, approval and review points; automatic generation of complex documents and letters; and full integration with DFM's visiting scientist salary payment system. This system will be phased in over the next few years with the first phase supporting the data collection and salary processing aspects of the system.

As indicated in previous years, DMB will continue to assure early training of its technical staff to take full advantage of preferred techniques as they become available. The branch will continue to test network systems, data base managers, personal computers, file servers, etc., and provide the lead in developing applications for use.

VAS

Laboratory of Applied Studies

John E. Fletcher, Chief

The Laboratory of Applied Studies (LAS) is a multidisciplinary laboratory made up of physicians, mathematicians, engineers and computer scientists; any or all of the disciplines represented may be brought to bear upon a given task. The Laboratory's approach to research problems is to examine the underlying scientific principles, identify the relevant mathematical and engineering concepts, and utilize computing systems to carry out research objectives. Many projects in this laboratory are collaborative efforts with bench scientists and clinical investigators at NIH or other research centers. Investigations range from direct involvement in clinical and laboratory activities, to the abstract development of mathematical methods and computer algorithms essential to quantitative computer modeling. The resulting software is made available as a general research tool.

Administratively LAS comprises two sections: the **Medical Applications Section,** including physician-scientists, electronics engineers, and computer systems analysts; and the **Applied Mathematics Section,** made up of specialists in applied mathematics, computer science and computer modeling. LAS projects also often involve guest workers and student or other volunteers.

Progress: Independent and Collaborative Projects

FY88 was a transition year for LAS as well as for DCRT. The continued emphasis on and increased capability of desktop computer systems has led our efforts in this direction. Distributed computing with up-load and down-load capability, the DCRT network, and a local area network within the laboratory enable us to link up with various levels of computing power from desktop personal computer (PC) to mainframe with vector capability. LAS began replacing its older IBM PC-XT systems with the new Personal System/2 (PS/2) systems in FY87 and should complete the process in FY88. New software capability, including on-screen edit and display of mathematical text and desktop publishing systems enables us to generate manuscripts on floppy disks or diskettes from which typesetting can be done directly, and to prepare publication quality text within the laboratory.

The applied mathematics activities were expanded in FY88. The extension of the algorithms for solving evolution equations to systems with weak nonlinearities was successful on both the mainframe and PC for advancing research on monoclonal antibodies. This process is being generalized for arbitrary systems of two reaction-diffusion equations. The mainframe PDECOL software was also modified to treat the same class of problems. Both the PDECOL method and the Crank-Nicholson method were found to give the same numerical results, providing independent validation of computed results from two different techniques. Applications to the monoclonal antibody studies have been presented at national conferences.

The NIH-wide Image Processing Group was organized by LAS in FY84 to increase communications and promote interaction among the many branches/laboratories involved with digital image processing. This group has sponsored a series of seminars in FY88 on a wide range of topics, including uses of advanced mathematical, topological and statistical methodologies. Seminar presentations included: the psychophysics of perception, texture discrimination, two-dimensional and three-dimensional imaging systems, adaptive segmentation, electron microscopy and control of motion artifact in cephalo-PET scans. This group has also published a list of image processing facilities at NIH with descriptions of hardware, software, areas of application and principal contact persons.

Biomedical signal processing activities in LAS have continued apace in FY88. Dr. J.J. Bailey addressed a meeting of the European Consortium on Common Standards in Quantitative Electrocardiography (CSE) on the subject of determining significant differences in the performance of diagnostic ECG algorithms. A paper on this subject was subsequently presented to the Computers in Cardiology conference in Belgium. Through studies of the CSE database of ECG's, the method for determining significant differences in the performance of diagnostic ECG algorithms was improved. This improved method was presented to the 1988 Conference on Computerized Interpretation of the Electrocardiogram.

A study which correlated ECG findings with histopathologic changes in chronic Chagasic myocardiopathy was prepared in FY88. This work was accomplished using the LSI-11 based system for analysis of physiological signals.

Investigation of signal processing methods on PC-based systems continued in FY88. MATLAB was shown to be particularly useful in the design and testing of digital filters. A study of digital filtering techniques applied to ECG's was presented at Computers in Cardiology.

FY88 featured a narrowing of LAS clinical collaborations as the result of the loss of medical staff fellowship positions. This reduction of staff has curtailed in-house development of the Neurological Monitoring System and led to an off-site transfer of this project. The equipment and software were integrated into a collaborative project with the Department of Neurosurgery at the Cleveland Clinic to test and further develop the system's capabilities in a clinical setting.

Nonparametric tests were performed on parameters derived from a cardiac scintigraphy database which included normal, focally abnormal and diffusely abnormal cases. The method used, which is based on the receiver operating characteristic curve, allowed simultaneous, unbiased evaluation of the sensitivity and specificity of the parameters being compared. This methodology was presented at Computers in Cardiology.

PC-based image processing systems are becoming more prevalent. The system which LAS assembled last year for a collaborative project with Children's Hospital to study spinal cord tissue trauma in animal models has been copied and installed for the collaborating neurosurgeon. Unlike dedicated image processing systems, the LAS system can also serve standard PC functions such as word processing, data base analysis and spread sheets.

R. Shrager serves as consultant to NIH biochemists in areas of data analysis, particularly in areas involving curve-fitting and digital filtering.

M. Douglas serves as a consultant in the field of image processing—both specific PC-based image processing for the DCRT Personal Workstation Office (PWO) and general applied image processing. Representing DCRT as vice-chair of the NIH Women's Advisory Committee, she has adapted their Career Network database to run under dBASE on the PC, assisted in their annual Career Day, and prepared their Problem and Barrier Identification report to the Division of Equal Opportunity (DEO). She also serves as DCRT representative to the Handicap Program Manager, DEO on computer access for the handicapped. She organized volunteers to staff the NIH Centennial Open House and developed the campaign for the 1988 NIH savings bond drive. For three months she served as temporary DCRT information officer in the absence of the information officer and public affairs specialist.

J. Fletcher serves as chairman of the Mathematics and Computer Science Department of the Foundation for Advanced Education in the Sciences (FAES), and was active as a consultant in mathematical methods and software for partial differential equations.

J. Bailey serves as consultant on Common Standards for Quantitative Electrocardiography, a program in medicine and public health sponsored by the European Economic Community, and also as a member of the American Heart Association Committee on Electrocardiography and Cardiac Electrophysiology. He is chairman of the Advisory Committee to the American Heart Association on computers and electrocardiography and secretary-treasurer of the International Society for Computerized Electrocardiography.

Future Projections

In collaboration with NIAID, a project has been designed to provide an interface between researchers utilizing the various molecular biology databases and the computer programs which carry out analyses of these data. Need for the interface was established in FY86-88 through consultation with researchers and others engaged in providing similar capabilities and through a review of the existing literature on this subject.

The molecular biology applications management system will be developed to interpret user specifications of sequences or subsequences for input to the various applications programs. The system will include a number of utility functions, as well as the production of output which will facilitate the understanding of a sequence and which also can be used to specify input for the program itself.

The applied mathematics section will continue activities in areas of laboratory computer applications, mathematical modeling and numerical integration of differential equations representing models in biology. The emphasis will be on software that can run on the new PS/2 systems.

Systems capable of delivering increasing amounts of image data are continually being added to the Nuclear Medicine Department. LAS collaboration in the development of fast interactive algorithms for the analysis of this data continues to be a priority task, as is the related problem of multimodality registration.

The necessary hardware for satisfactory image processing on PC's is becoming available. This will greatly increase use of PC's for a number of image applications. The development of data analysis systems, using both the mainframe and the PC will be continued next year. The use of the PC with appropriate mathematical analysis software will be promoted as an alternative to older mainframe software, which is becoming obsolete. In addition, newly developed hardware and software may be acquired to make the PC a more useful data analysis tool for laboratory use.

Efforts to survey the use of mathematical modeling of the human immune system to understand the destructive effect of the AIDS infection will continue in FY89. Quantitative data are needed on the parameter values for use in model simulations. Emphasis will be placed on collaborations with laboratory investigators to guide the appropriate simulation studies.

Refinement of a neurological monitoring system for critically ill neurosurgery patients will be undertaken in FY89. Analysis algorithms will be refined to identify more accurately cerebral ischemia or hemorrhage, and the display will be augmented to enable separation of normal and abnormal data interactively. This study will be conducted concurrently with additional animal studies in rats.

A new project in biosignal analysis involving the correlation of heart rate variability (HRV) with parasympathetic/sympathetic tone in free-living simians will be pursued in collaboration with the Laboratory of Comparative Ethology (NICHD). New methods will be devised using MATLAB implemented on the IBM PC-XT to minimize confounding factors such as muscle noise, artifact and extrasystoles, which interfere with an accurate determination of HRV.

Research Projects

Computer Systems for Nuclear Medicine

Margaret A. Douglas

with: James J. Bailey, M.D. (DCRT/LAS); CC/Nuclear Medicine; NHLBI/CB.

LAS is developing systems for computer-based mathematical analysis, pattern recognition and image processing in support of diagnostic activities in the Nuclear Medicine Department of the Clinical Center and collaborating Institutes. Diverse applications include: parameters of ventricular function extracted from radionuclide ventriculography, tumor detection and imaging utilizing radio-labeled monoclonal antibodies and functional imaging of the central nervous system using PET scan technology. The correlation of function as obtained from PET scans with structure as revealed by CT and MRI scans is an important effort. Various general purpose image processing facilities for the Nuclear Medicine Department are being evaluated, including the possibility of implementing PIXAR or ANALYZE on a Sun 4 Workstation.

Nonparametric comparison via receiver operating characteristic (ROC) curve plots have been performed for various parameters and combinations of parameters of a cardiac function test. These measures of cardiac function were derived from an existing cardiac scintigraphy data base consisting of three groups (normal, focally abnormal and diffusely abnormal). The nonparametric test allows simultaneous, unbiased evaluation of all levels of sensitivity and specificity for the parameters being compared on the same patient population.

The general purpose image processing system, MIRAGE, has been completed. A three-dimensional imaging capability has been designed and specified to work in conjunction with MIRAGE. The Nuclear Medicine Department has acquired a Posicam scanner, an advanced-state PET scan capable of gated acquisition of 21 simultaneous 256 x 256 slices per second, i.e., over one million events per second. Development of fast interactive algorithms for analysis of this data is an ongoing task.

Other applied image processing activities include investigating automated cell classification from micrographs; campus-wide consulting on image processing, especially in the area of PC-based image processing; consulting on the related topic of PC scientific graphics; and investigating PC CAD. LAS personnel also conduct seminars through the NIH-wide Image Processing Group, review the field of medical image processing of micrographs for an invited journal review article and serve as image processing representative to groups involved with NIH campus computer connectivity.

Computer-based Analysis and Image Processing in Electron/Light Microscopy and X-ray and Electron Energy Spectroscopy

Margaret A. Douglas

with: Dennis Johnson, M.D. (Children's Hospital).

This project is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally X-ray micrography and electron energy loss spectra, and the electron/light microscopy images of biological specimens.

In a collaborative project with the Department of Neurosurgery at Children's Hospital, light microscopy is being used to study rodent spinal cords to determine parameters of injury (i.e., loss of axon volume, number of axons, inflammatory infiltrate, etc.). Examination of a large number of specimens and estimation of objective parameters requires efficient and sophisticated image processing. Commercially available software and hardware have been assembled into a system and tested. After a year of successful use, the system was duplicated so that both LAS and Children's Hospital have comparable systems. Additional software has been written this year that detects individual axons, counts them, and adds new results to existing files. This method has been tested on existing micrographs and will be tested on additional micrographs of spinal cord sections after trauma for validation.

Interface for Computer Analysis of Molecular Databases

Martha R. Horton

with: Philip Krause, M.D. (IRP/LCI/NIAID); James J. Bailey, M.D. (LAS/DCRT).

A survey by LAS in FY86-88 indicated a clear need for assistance to researchers using the wide variety of programs developed to manipulate sequence data and the wide variety of data structures which these programs use. Many of these programs are difficult to execute; others are easier to use but are severely limited in options.

For example, the system may not accommodate the format of the database that the investigator wishes to query, or it may not have the flexibility to display all levels of data from local sequences (nucleotides or amino acids) up to diagrams of the entire macromolecule. Therefore LAS has initiated a project to create a molecular biology applications management system that would give scientists easier use of these databases and improve access of the analysis programs.

The planning phase is near completion and active development of the interface has begun. A preliminary grammar for the interface has been formulated and development of the software to parse and translate the query commands is underway.

The design of the interface will permit easy extension and expansion as desirability for additional capabilities is recognized. An integral feature of the interface will be display of pertinent sequences from the databanks on both screen and hardcopy, and in formats which will be useful "maps" for the reader seeking specific strings in a large volume of data.

Computer-Based Monitoring of Central Nervous System (CNS) Function in Intensive Care

Martha R. Horton

with: R.C. Burgess, M.D., Ph.D. (Cleveland Clinic Foundation, Department of Neurology).

Evaluation of the integrity and function of the CNS in critically ill patients with ischemic, metabolic or traumatic brain insults is ordinarily assessed by episodic neurologic exams and cannot be done in an ongoing fashion. This project is designed to develop and test a computer-based system for acquisition, analysis and display of scalp-recorded, neuroelectric signals (electroencephalogram and evoked potentials). This tool can be used to investigate the degree of dysfunction in neurologically impaired patients, to correlate the indices developed with other measures of cerebral function and to evaluate the effectiveness of various therapeutic interventions. The system automatically sequences from one stimulus modality to the next while simultaneously adjusting preamplifier/filter parameters, generating cumulative displays and saving the results for trend analysis. Programs for digital filtering, frequency domain analysis and displays using color to highlight important trends have been implemented.

During the past year, studies on a canine model of septic shock have been completed, and the CNS monitoring system has been transferred from the animal laboratory to begin clinical evaluation at the Cleveland Clinic Foundation where collaborative studies are now being pursued. Software is now being developed to permit the clinician to perform cluster analysis based on a small number of sensitive, non-linear parameters. This is accomplished through the display of multiple parameters two-by-two, and the use of interactively specified groupings which are clinically meaningful. Selected thresholds are stored by the computer for future processing.

In a separate activity to be continued in FY89, The Cleveland Clinic Foundation has begun to study cerebral ischemia and hemorrhage in a rat model. The CNS monitoring system developed by LAS will be the sole measure of neurophysiologic function in the evaluation of rheologic and pharmacologic treatment of this disorder. As in the earlier dog experiments, CNS indices will be compared in vivo with continuous hemodynamic and cerebral perfusion measurements. At necropsy, histological examination and double labeled autoradiographs will be used to compare efficacy in 50 animals from each therapeutic group.

Mathematical Models of Binding Equilibria

John E. Fletcher, Ph.D.

with: Ernest Richards, M.D., Department of Nutrition, Rutgers University, Brunswick, N.J.

LAS is conducting a study of mathematical models of ligand-receptor or ligand-macromolecule binding studies at equilibrium. Appropriateness of various model fitting criteria are studied and general guidelines and computational algorithms are designed for computer-aided interactive model fitting.

During FY88, a study was made of the binding of 16-[9-anthroyloxy] palmitoyl-CoA to BSA. Computer programs capable of doing the general binding analyses were supplied to the Rutgers University Computer Center. A manuscript describing the binding analyses has been submitted for publication.

The Solution of Reaction Diffusion Systems in Biology

John E. Fletcher, Ph.D.

LAS is developing numerical methods and mathematical software to solve ordinary and partial differential equations that describe dynamic physiological processes.

During FY88, a method for solving a single reaction-diffusion equation was extended to a system of two such equations with general boundary conditions and with weak nonlinearities. At the same time, a general program, PDECOL, was adapted to solve the same systems. This dual approach provided system validation. Since no exact solutions existed, the same results produced by independent numerical techniques provided a check on the computed results. Presently these systems are being adapted for PC use. Despite problems with obsolete equipment and software, and personnel turnover, progress has been made on the monoclonal antibody study. A publication on the solution of the capture time equations for ultracentrifugation is in press.

In FY88, emphasis has shifted to two extremes: software capable of operation on the mainframe facility, and software that can run on a PC-based system.

PDECOL has exhibited undesirable error levels for some evolution equations and new procedures are being investigated to improve solution accuracy. A second problem encountered with PDECOL is an inability to handle inconsistent initial and boundary conditions. This is a common occurrence in physical models but is not handled by many commercially available programs. New algorithms are being investigated to solve these problems.

Cellular Kinetics Models of the Human Immune System (An Investigation of HIV-like Infections in a Model Immune System and its Response to Opportunistic Pathogens)

John E. Fletcher, Ph.D.

with: James J. Bailey, M.D., Richard I. Shrager, M.S. (LAS/DCRT); William L. Jackson, M.D., Ph.D. (NIDR/LOM/CIPCB).

LAS is engaged in modeling the cellular kinetics of the immune system, including interactions of T-lymphocytes (helpers, cytotoxic and suppressor cells), B-lymphocytes, macrophages and cytokines (interleukins, interferons, colony stimulating factors, etc.). Models are expressed in the form of systems of nonlinearly coupled differential equations. By using a simulation that can examine a retrovirus-like infection, we hope to better understand how AIDS cripples the immune system and eventually compromises its ability to respond to other opportunistic pathogens. Appropriately constructed and validated models may predict how the immune system will respond to therapeutic interventions and vaccines.

Of critical importance is that models reflect accurate experimental data and reliable parameter values. The collection of such values has been the primary function of this activity to date. Some abstracts have been presented on preliminary versions of the model and some parametric studies have been conducted that illustrate the model's behavior. The parameters and parametric studies will be refined as our understanding of the various cell kinetic interactions improve. Closer collaborative relations with laboratory and clinical investigators to aid in the refinement process are being pursued.

Computer-Aided Analysis of Electrocardiography

James J. Bailey, M.D.

with: M.R. Horton, R.I. Shrager (DCRT/LAS); G. Campbell, Ph.D. (DCRT/LSM); Framingham Heart Study (NHLBI), Cardiology Department, Bowman-Gray School of Medicine; University Hospital St. Rafael, Leuven, Belgium.

Studies are being conducted on evaluation of the prognostic power of the electrocardiogram when analyzed by advanced computer methodology and the predictive accuracy of ECG criteria when implemented in ECG computer programs. The use of well documented populations and multivariate statistical techniques in designing new criteria are also under investigation.

Studies in collaboration with NHLBI and the Framingham Heart Study and in collaboration with personnel conducting the National Health and Nutrition Examination Survey (NHANES) for the National Center for Health Statistics have been published in the *Journal of Electrocardiology.*

A paper describing the determination of statistically significant differences in the performance of ECG diagnostic algorithms was presented to Computers in Cardiology in Belgium. This method, based on McNemar's test, assumed extreme limits for Kendall correlation in order to estimate areas of significance and nonsignificance. Between these two was an area of uncertainty that required knowledge of the correlation. Subsequently data was obtained from the CSE study in which several readers and computer programs analyzed 250 ECG's. From these data, more realistic estimates on the limits for Kendall correlation were derived. This allowed the area of uncertainty to be reduced by two-thirds. This study was presented at the 1988 Conference on Computerized Interpretation of the Electrocardiogram.

Dr. W.K. Haisty at Bowman-Gray University is devising a method to translate digital ECG data received on cassettes from Framingham into a format usable at DCRT. Until this is accomplished, the population studies with the Framingham data cannot proceed.

Mathematical and Computational Methods for Solving Nonlinear Equations

Richard I. Shrager

with: P. Thall, Ph.D. (GWU/STAT); R. Simon, Ph.D., S. Ellenberg, Ph.D. (NCI/DCT); W. Hoffman, M.D. (CC/CCM); R. Burgess, M.D., Ph.D. (Cleveland Clinic); J. Fletcher, Ph.D. (DCRT/LAS) G. Campbell, Ph.D. (DCRT/LSM); R. Winslow, M.D., M. Marini, Ph.D. (LAIR Blood Res.); P. McPhie, Ph.D. (NIDDK/LBM); E. Korn, Ph.D., R. Hendler, Ph.D. (NHLBI/LC).

LAS is developing mathematical and numerical methods for solving nonlinear equations frequently encountered in NIH research activities. These equations usually appear in the context of constrained nonlinear least squares problems, or in the numerical solution of nonlinear differential equations. Related problems, such as asymptotic error analysis and the efficient treatment of sparse matrix systems are also considered. Software packages that result from these developments are made available as general research tools.

In FY88, collaborative investigations:

- Analyzed circular dichroism data from swine pepsinogen by singular value decomposition.
- Developed a kinetic model for actin-actobindin interaction. Actin plays a major role in determining the structure of the cytoplasmic matrix of most nonmuscle cells.
- Consulted with Letterman Army Institute Research (LAIR) Blood Research group on the use of software developed at DCRT for modeling hemoglobin binding to various ligands.
- Published a two-stage design for clinical trials at NCI that required optimization and mathematical analysis techniques.
- Developed and presented a comparative study of robust methods for the one-parameter estimation problem.
- Presented work on tracking the spectral edge frequency of an EEG. This work was also submitted for publication and is in press.

In FY89, robust estimation studies will be extended to the two parameters in the Michaelis-Menten rate model, which was used in several previously-published studies. Hemoglobin modeling software will be modified to allow for the automatic rejection of species (e.g., sulfoxy-Hb) which are not present in detectable levels. Evaluation of the spectral edge frequency tracking methods will be extended by the inclusion of new animal data. The actin-actobindin model contains hundreds of differential equations and is unmanageable in its present form. The simplified actin model on which it is based is often reduced to only two approximating equations. The behavior of the larger model will be studied with the goal of drastically reducing the number of equations to those essential to model the filament formation.

Analysis of Physiological Signals

E.W. Pottala, Ph.D.

with: J.J. Bailey, M.D. (DCRT/LAS), J.A. Dvorak (NIAID/LPD), K. Rasmussen, Ph.D. (NICHD/LCE).

The development and application of minicomputer and PC-based signal processing techniques for analyzing physiological signals, e.g., electrocardiogram, electromyogram and electroencephalogram continued in FY88. The LAS minicomputer-based system provided a general A/D facility and ability to filter the signals with a variety of analog and digital techniques. In FY87 the aged

(17 years) MAC-16 system was replaced by an LSI-11-based system which increased facility for appending filenames, editing and programming in FORTRAN.

Digital and analog signal processing techniques have been applied in the past to electrocardiograms from the NIH Clinical Center, the Framingham Heart Study and Georgetown Medical Center; to electromyograms in fatigue studies with the National Institute of Occupational Safety and Health and in myasthenia gravis studies with NINCDS; and to blood pressure and electrocardiograms in simian models of cardiovascular dynamics with NHLBI. More recently (FY86-88), these techniques have been applied to electrocardiograms in a murine model of Chagas' disease with NIAID. A paper was published in FY87 and another is in preparation which correlates changes in the electrocardiogram to the histopathological findings in the chronic disease state.

In FY88 a new project was undertaken to analyze heart rate variability (HRV) on free-living simians studied by investigators at the Laboratory of Comparative Ethology (NICHD). New methods need to be devised to control muscle noise, artefact, extrasystoles and other confounding factors which may interfere with obtaining an accurate measure of HRV in the frequency domains. Review of the literature reveals that the power of HRV in the 0.1-0.4 Hz range is related to parasympathetic tone in the resting animal. However, power below 0.1 Hz may be related to complex combinations of parasympathetic tone, sympathetic tone and baroreceptive reflexes in the active state.

Also in FY88, some signal processing activities were shifted from mainframe or minicomputer to PC, using MATLAB, a matrix manipulating software package implemented on the IBM PC-XT. This system was used to compare the advantages of preprocessing ECG data with digital high pass filters versus using a cubic spline to subtract out estimated baseline wander. A paper describing this study was accepted for presentation at the Computers in Cardiology conference. This system provides a flexible, easy-to-use and inexpensive facility for interactive design of digital processing techniques and display of results.

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LSM

Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Ph.D., Chief

The Laboratory of Statistical and Mathematical Methodology (LSM) combines research in mathematical statistics, mathematics and computer and information science with collaboration and service in these areas for NIH researchers and administrators. LSM staff interact with all NIH Institutes, other Federal agencies outside HHS and biomedical researchers worldwide.

In addition to the chief, the laboratory has ten full-time professionals, including research mathematicians, mathematical statisticians, computer systems analysts, and programmers, in four sections:

- **Statistical Software Section** (SSS) provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis including selection and support of large systems and packages.
- **Statistical Methodology Section** (SMS) works closely with the Statistical Software Section, providing biostatistical consultation and DNA analysis software tools. It also conducts independent research.
- **Biomathematics and Computer Science Section** (BCS), performs independent research and provides consultation in mathematics and on software used for scientific printing and graphics.
- **The Medical Information Science Section** (MIS) investigates and develops methods for application of information and computer science to medical language data processing.

Computation in FY88

A major part of LSM activity is offering statistical, mathematical and other scientific systems and packages to the NIH user community. LSM staff evaluate new systems and packages for suitability to NIH needs.

LSM support always includes maintenance of the system or package, with adequate documentation, which includes NIH computer system changes, system or package updates, and corrections. It also includes rapid response to queries concerning user access to the most used systems and packages, including job control language, program parameters or other operating system procedures and assistance in interpretation of results.

LSM recognizes the importance of teaching the effective use of systems and packages to biomedical researchers and other NIH users, and maintains a substantial program of short courses, documentation preparation and informational talks and articles. Computer systems and packages supported by LSM are shown in Table 1. Use of these statistical packages at NIH since 1975 is shown in Figure 1.

As in previous years, the statistical and data management system, SAS, is extensively used at NIH, with an average of 87,400 IBM System 370 accesses per month, up from 82,700 accesses per month in FY87. LSM taught eight introductory courses for SAS, three courses for SAS/GRAPH, and four Permanent SAS Files courses. The SSS staff answered over 10,000 calls for SAS assistance. The average number of accesses per month for SPSS-X was around 3500, down from 4000 per month in FY87. The BMDP package averaged 680 accesses, down from 1000 in FY87. Three new SAS products were supported in FY88: SAS/AF, an application facility; SAS/IML, a powerful interactive matrix language; and SAS/CBT, a computer-based training course. SPSS-X and IMSL went through a major release change.

Other software supported by LSM has more limited use—from an estimated 800 GRAPH sessions, 500 MLAB sessions and 250 VMAP accesses per month, down to relatively few sessions for specialized programs such as REDUCE, DNALAB, GLIM and CART. Several seminars on GRAPH use were held. Conversion of GRAPH to the C language, for microcomputer and minicomputer implementations of the program, has begun.

This year two members of LSM received Special Achievement Awards from the Clinical Center for their work in revising LSM's interview scheduling system for Medical Staff Fellows.

Consultation, Collaboration and Research in FY88

The staff of the Statistical Methodology Section provides consultation in a wide range of scientific fields, and interpretation of the results of statistical and other scientific computation. Consultations can be brief or extensive depending on the complexity of the statistical or scientific research. Research projects in LSM vary widely; they include studies employing statistical methodologies for biomedical applications, studies of language processing for medical information systems, studies of scientific computer printing and graphics and research in mathematical and statistical methods.

Table 1. Systems and Packages Supported by LSM.

SAS, SAS/GRAPH, SAS/ETS, SAS/OR, SAS/FSP, SAS/AF, SAS/IML, SAS/CBT
Vendor: SAS Institute, Inc. A batch and interactive IBM S/370 system for statistical analysis, with extensive file manipulation capabilities and graphics, also in interactive mode on the IBM PC-XT or PC-AT.

SPSS-X, SCSS, SPSS-PC
Vendor: SPSS, Inc. A system for univariate and multivariate statistical analysis with file handling capabilities, in batch mode on the IBM S/370 and DEC-10, and interactive mode on IBM S/370, DEC-10 and IBM PC-XT or PC-AT.

BMDP
Vendor: BMDP Statistical Software, Inc. A collection of IBM S/370 batch programs for univariate and multivariate statistical analysis.

P-STAT (Princeton Statistical Package)
Vendor: P-STAT, Inc. A system for statistical calculations and file manipulation, in interactive or batch mode on the IBM S/370.

IMSL (International Mathematical and Statistical Libraries)
Vendor: IMSL, Inc. An extensive collection of FORTRAN routines for statistical and mathematical analysis, for IBM S/370 or DEC-10 batch computation.

MSTAT 1
Source: DCRT staff. IBM S/370 batch programs and subroutines for mathematical and statistical analysis.

GLIM (Generalized Linear Interactive Modeling)
Vendor: Numerical Algorithms Group, Inc. An IBM S/370 batch and interactive system for analysis of linear statistical models.

CART (Classification and Regression Trees)
Vendor: California Statistical Software, Inc. An IBM S/370 batch and interactive system for tree-structured regression and classification analysis.

GRAPH
Source: LSM staff. An interactive DEC-10 program for preparing a wide variety of graphs of scientific data.

DNA:DRAW
Source: LSM staff. An interactive DEC-10 program for preparing publishable displays of DNA sequences.

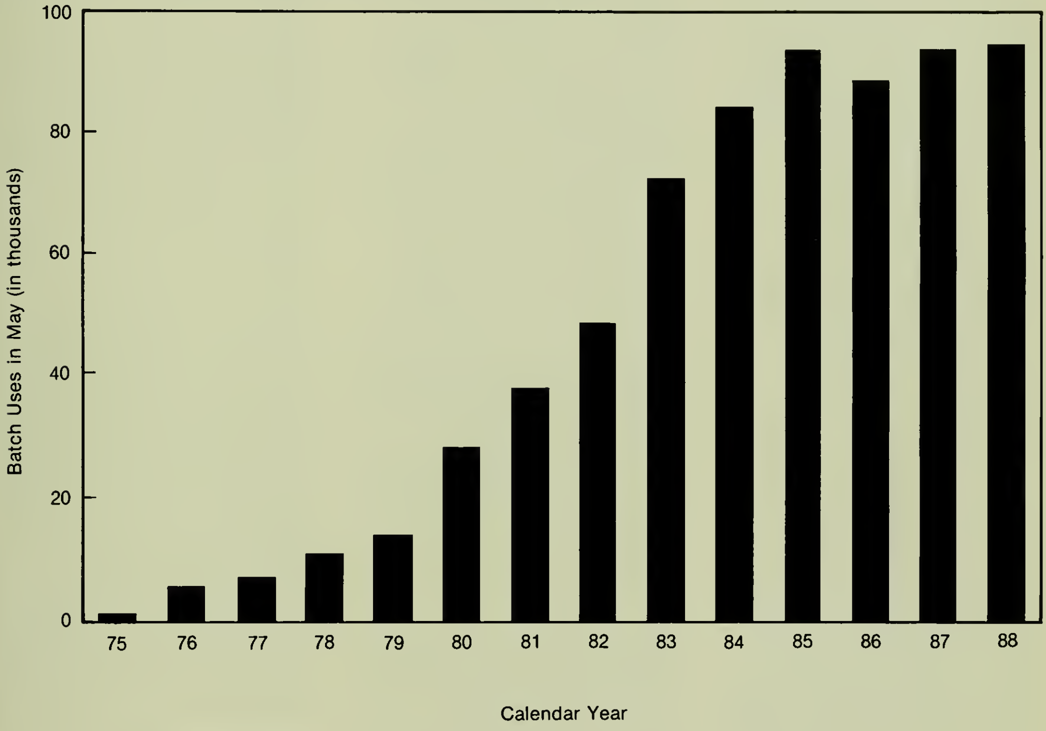
DNALAB
Source: LSM staff. An interactive DEC-10 program for graphically displaying effects of restriction enzymes in cloning experiments, locating possible exon splicing sites, and analyzing DNA sequences available from data banks.

MLAB (Modeling Laboratory, including C-LAB)
Source: DCRT staff. An interactive DEC-10 system for curve-fitting and analyzing functional or differential equation system models, with many cluster analysis and other mathematical operators, and publication quality graphics.

VMAP
Source: LSM staff. An IBM S/370 batch program used for printing scientific text and diagrams. It is used in conjunction with the WYLBUR text editor and IBM 6670 laser printers.

REDUCE 3
Source: Rand Corp. An interactive DEC-10 system used for symbolic and algebraic manipulation of mathematical formulas.

Figure 1. Use of Statistical Packages Supported by LSM/SSS.



During FY88, SMS staff were active in mathematical statistical research in a variety of areas.

Studies of size and shape variables continued. These studies provide methods for studying random proportions or ratios of common occurrence in biomedical data. A paper on application of lognormal distributions to fundamental models of biological growth using size and shape concepts appeared this year. Dirichlet covariate models were enhanced and computer programs were developed. A paper on this topic appeared in the *Proceedings of The Section on Statistical Graphics of the American Statistical Association*. This work was presented in talks at the State University of New York at Stony Brook, the University of Montreal and the Johns Hopkins University.

The study of the problem of optimal unbiased estimation of variance components in mixed models with possibly unbalanced data was continued and expanded. A visiting researcher has arrived for the purpose of implementing methodologies based on LSM research results in studies of genetic heritability and gene linkage. This research will include the preparation of PS/2-compatible computer programs. Additionally, theoretical results continued to appear. A paper on algebraic methods applied to mathematical statistical problems in component estimation appeared, and another more fundamental paper in algebraic methods has been accepted for publication. Invited lectures on these topics were given at eleven universities in the past year.

Investigations in nonparametric statistics continued. A study of the robustness of weighted estimators of location using computer simulations was completed and is in press. Work on inferential procedures for correlated proportions was continued and presentations on this topic made with application to ECG program evaluation were made in Belgium and the United States.

A comprehensive study of Receiver Operating Characteristic (ROC) curves was begun. The ROC curve is an important tool in the evaluation of diagnostic biomedical tests. A nonparametric approach has been developed to compare two diagnostic ROC curves in the important situation in which the same patients are used for both tests. A parametric model based on fitting the ROC curve using truncated exponential distributions has been developed which is robust and provides a guide for the treatment of ties. Numerous applications of this methodology to ECG programs and to radiology are being studied. Presentations on this research were made at Liege and Namur in Belgium, and at the American University, Washington, D.C.

During FY88, the staff of the Biomathematics and Computer Science Section spent considerable time expanding and developing the local area network facilities available to LSM staff. The hardware configuration more than doubled in size this year, with the addition of six microcomputers and three diskless workstations. A number of special printing facilities were added. The interim version of VMAP is now available to LSM staff on the network, and a version for the HP LaserJet II printer is now being tested. In cooperation with members of SSS and SMS, BCS staff prepared special printing facilities for immediate printout of SAS reports of publication quality by a network printer. Some BCS staff time was devoted to testing software for the Advanced Laboratory Workstation Project led by DCRT's Computer Systems Laboratory.

BCS mathematical research on the algebra of rings and modules continued, with several publications appearing this year. One paper provided a solution to all free word problems for additive relation algebras of modules. Another paper currently in press treats the existence of certain functions relating various categories of modules.

In MIS, research in medical linguistics continued, but at a reduced level due to loss of staff. A parsing methodology based on a predicate calculus formalism is being implemented. A separate project for development of a comprehensive lexicographic data base will be continued, and used as a system facilitating collaborative research. LSM continued collaboration with the Laboratory of Pathology, NCI/DCBD/LP, and DCRT/DMB, in using LSM's automatic encoding system to maintain and improve the surgical pathology report data base of the Clinical Center. In a number of instances MIS staff assisted in the formulation of special queries for this data base.

Future Plans: Software Development, Contracts, Network Devolopment

Laboratory service and research will be maintained as availability of staff permits. LSM's high level of support for IBM S/370 statistical software systems will be continued. Current levels of systems/packages support, consultation and user support will be maintained as much as possible. Contract support for MLAB will continue at a reduced level. Adaptation of GRAPH, DNADRAW and VMAP for use on the PWO-supported network will continue. Further development of VMAP is anticipated.

LSM will expand its contribution to software testing and development for two DCRT local area computer networks: A network supporting IBM compatible and Macintosh microcomputers, and the Advanced Laboratory Workstation Project of CSL supporting Unix-based workstations. Support of SAS in a PC/networking environment will also be expanded.

Research Projects

Automated Data Processing of Medical Language

G. Dunham

with: A. W. Pratt (DCRT/OD); M. G. Pacak (Guest Researcher), S. Harper (DCRT/LSM); E. Jaffe (NCI/DCBD).

The major objective of this project is the development of methods for the automatic processing of natural medical language. This involves both development of algorithms for parsing and representing natural text, and creation of computer dictionaries and other data bases for medical specialties such as surgical pathology.

Research in medical linguistics continued on the development of a theorem prover for a higher order predicate calculus, constrained by assumptions associated with relevance/entailment logic, as a vehicle for parsing in a head-feature based grammar formalism.

Collaboration continued on the Clinical Information Utility with the Laboratory of Pathology, NCI/DCBD/LP, and with DCRT/DMB, in using LSM's automatic encoding system to maintain and improve the data base of Clinical Center surgical pathology reports. Transition from word processors to the Clinical Center MIS for producing the surgical pathology reports is near completion.

Development of the Lexicographic Environment Software continued but at a reduced pace. This is designed to provide medical lexicographers and medical language researchers with a comprehensive tool for examining data and testing hypotheses, as well as for constructing both semantic and syntactic features of medical dictionaries.

Computer Graphics and Applications

M.B. Shapiro

The main objective of this project is the application of computer graphics and related methods to NIH research problems.

The GRAPH and DNADRAW programs, heavily used on the DECsystem-10 computer for the past five years, are being rewritten for the IBM PC/AT, and PS/2's (models 60 and 80). This involves not only reprogramming, but considerable redesign of the earlier system. The C language is being used, so that the programs should be portable to other machine environments with a minimal amount of additional work. At present, about one-third of the GRAPH program has been completed and a much superior version of the FORMAT option of DNADRAW is now running on the PC.

Consulting has been done mainly with users of the DNADRAW program. In addition, work was done with Dr. Roger Miller of NIAID to predict the location of splice sites in genes coding for the Hepatitis B virus.

Discrete Mathematics and Applications

G. Hutchinson, Ph.D.

The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics and graph theory), and to apply such methods to appropriate problems of biomedical research and computer science.

Work continued on the characterization of rings which possess the same lattice theory. A joint publication was accepted for the *Proceedings of the American Mathematical Society.*

During the year, many improvements were made to the interim VMAP system for scientific printing, and versions for printing on the local area network and on a directly connected Hewlett-Packard LaserJet II printer were implemented. A contract for creation of public domain computer fonts was advertised. Further revisions of the design for a production version of VMAP accommodating this font system are nearing completion.

Analysis of lattices and categories of modules will continue. Production versions of the revised VMAP will be prepared for local area network operation and for directly connected laser printers. A production version of VMAP for the IBM system 370 will be implemented subject to availability of suitable printing facilities.

Multivariate Statistical Analysis

J. E. Mosimann, Ph.D.

with: G. Campbell (DCRT/LSM); E. Depiereux (Facultes Notre Dame de la Paix, Namur, Belgium).

The objective of this project is the study of multivariate ratios or proportions.

Studies of random proportions and ratios, including those which follow a multivariate lognormal distribution as well as those following the distribution of a mixture of Dirichlet distributions were continued. Presentations on this work were made at the State University of New York at Stony Brook, the University of Montreal, the Johns Hopkins University and at the International Meetings of the Biometric Society (Namur, Belgium).

A paper on applications of the lognormal distribution appeared this year. Studies relating size and shape analysis with correspondence analysis, and other generalizations of principal component analysis, were continued (with Dr. Eric Depiereux of the Facultes Universitaires Notre-Dame de la Paix, Namur, Belgium).

Present research studies are being undertaken with a view toward writing a monograph.

Linear Methods in Statistics

J.D. Malley, Ph.D.

with: W. Slanger Ph.D. (DCRT/LSM, and North Dakota State University); R. Elston (LSU Medical Center).

This continuing project will develop new methods in statistics, using algebraic techniques, that have applications for biomedical research.

Newly developed methods in variance component estimation, and estimation in models with linear covariance structure, were previously brought together and published in a book. Research on these methods continues, particularly with respect to applications in genetics and animal sciences. Algebraic methods themselves continue to be studied with one paper being published this year, and another accepted for publication. Further studies concern the use of Jordan algebras to solve the problem of estimation in the presence of missing data in the mixed linear model. This technique applies to repeated measures problems and longitudinal studies, both of much interest to the biomedical community. Computer programs to implement various theoretical methods are in preparation to facilitate the analysis of human genetic variation and inheritability using the results on optimal unbiased estimation for variance components.

Nonparametric Statistics

G. Campbell, Ph.D.

Work on proportional data, including the development of models for proportions with covariates, has proceeded with attention both to theory and computer implementation for applications. In the area of correlated proportions where the correlation is unknown or unreported, additional work has extended the theory from a lower bound of zero correlation to the practical situation in which previous data is used to impute a lower bound for the positive correlation and use this information in the inference. This has been applied to the evaluation of ECG algorithms.

In nonparametric and robust regression, the behavior of several robust and nonparametric estimators has been studied, with attention to the use of weights on the pairs of observations to improve the performance over the classic least squares estimates, for normal and other distributions. A simulation study has begun to evaluate various estimators in the one-sample location problem with known weights, which would arise if the different variances were known. A presentation at the Computer Science and Statistics Symposium on the Interface and a joint paper have resulted.

A comprehensive study of Receiver Operating Characteristic (ROC) curves has begun. As a plot of the probability of true positives versus that of false negatives according to varying rules, the ROC curve is an important tool in the evaluation of diagnostic biomedical tests. A nonparametric approach has been developed to compare two diagnostic tests using areas under ROC curves in the situation in which the same patients are used for both tests. In the case of a sparse number of points plotted on the empirical ROC curve, as usually occurs with ratings data, the straightforward nonparametric estimator for the area under the curve is biased in that the naturally occurring ties are not correctly treated. A parametric model based on fitting the ROC curve using truncated exponential distributions has been developed which is robust and has the additional feature that it serves as a guide for the treatment of ties within intervals, in order to reduce the bias of the nonparametric estimator. The numerous applications of this methodology to ECG programs and to radiology are being studied.

Consulting Services

J. E. Mosimann, Ph.D.

with: J. D. Malley, Ph.D., G. Campbell, Ph.D., G. Hutchinson, Ph.D., R. Danner, and M. Shapiro (DCRT/LSM).

LSM staff members provide consulting services in statistics, biomathematics and computer analysis of DNA sequences. LSM's consultation work includes the following:

- Dr. S. Altschul (NIDDK/MRB): LSM provided consultation on a graph theoretical solution of importance in the general problem of aligning and comparing DNA sequences.
- Ms. E. Goldberg (NIMH/MHIRP): Distinct patterns of performance of schizophrenic patients on the WAIS-R intelligence test were demonstrated through statistical comparisons of the schizophrenic patients' IQ scores against those of the standardization group.
- Dr. G. Cutler (NICHD/DEB): A variety of consultations were held with members of Dr. Cutler's Developmental Endocrinology Branch, dealing with treatment, detection and prevention of childhood and juvenile endocrinology problems. All of the studies involved repeated measures analyses suitable for the study of longitudinal data.
- Dr. D. Rabin (NICHD/DEB): LSM assisted in the analysis of measurements of mineral bone content using the two methods of photon analysis and ultrasound in groups of normal women and women with osteoporosis. The statistical analyses provided included logistic regression, discriminant analysis and ROC curve analysis.
- Dr. I. U. Ali, Dr. R. Callahan (NCI/LTIB): The association of the amplification of the oncogene c-erbB2 in human breast tumors with lymph node number and with survival was investigated. LSM contributed extensive statistical analysis using contingency tables, correlation and survival analysis to investigate this question using data collected by LTIB. In press there is both a Technical Comment for *Science* and an article for *Oncogene Research*.
- Dr. M. Jaffe, Dr. G. Straw (NIMH/MHIRP): A study of the electro-retinogram amplitude response of the dark-adapted a-wave of human subjects to different light intensities has been conducted. LSM has provided statistical expertise concerning the modeling of the data with the Michaelis-Menton and Hill equations using weighted linear and nonlinear regression techniques.
- Dr. D. Pontbriand (DRS/VR): LSM provided the expertise for the statistical analysis of the data for a study of motility and acrosomal integrity of ram sperm that had been frozen and then thawed by various cryogenic methods using a repeated measures design and multiple comparisons.
- Dr. T. Sherman (NIMH/LDP): Reaction times measurements were analyzed for symbol identification in the presence of distractors for normal patients and patients with schizophrenia. LSM designed and implemented a thorough series of statistical analyses involving weighted repeated measures designs.
- Dr. A. Cheever (NIAID/LPD): Schistosomiasis infections are studied in different strains of mice by different parasite strains. LSM assisted in data base management for experimental measures of levels of fibrosis, granuloma size and extent of infection; and provided advice and assisted in statistical analyses. A paper on the study appeared in volume 37 of the *American Journal of Tropical Medicine and Hygiene*.
- Mr. M. Anderson (NCI/DCPC/HPSB). LSM assisted in the editing of data collected through 30 cancer centers from 1983-1987, and facilitated in the preparation and analysis of SAS data sets.
- Consultations on the use of the DNADRAW program, for producing publication quality drawings of DNA sequences, included the following:

Dr. S. Cheng (NCI/DCBD);
Dr. L. Hennighausen (NIDDK/LCM);
Dr. G. Hollis (NCI/DCT/COP);
Dr. B. Patterson (NCI/DCE/LB);
Dr. S. Tronick (NCI/DCE/LCMB);
Dr. R. Wickner (NIDDK/LBP).

- Consultations on the use of the GRAPH program for producing publication quality graphs were numerous and included consultations with:

Mr. J. Aarons (NIMH/MHIRP);
Ms. J. Guroff (NIMH/BP);
Dr. A. Leroy (DRS/BEI);
Dr. A. Minton (NIDDK/LBP);
Dr. W. Stewart (NIDDK/LAC);
Dr. J. Zimmerburg (NIDDK/LMB).

Consulting services will continue with available staff. Due to staff reductions, biomathematics consultation will be very limited.

Publications and Presentations

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Campbell, G.: Statistical Techniques for the Detection of Differences in the Performance of ECG Diagnostic Algorithms. Dept. of Medical Informatics, University of Leuven, Leuven, Belgium, July 14, 1988.

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Malley, J.: Jordan Algebras and the EM Algorithm for Patterned Covariance Matrices. University of Maryland, College Park Campus, Department of Mathematics, College Park, Maryland, February 4, 1988.

Malley, J.: Jordan Algebras and Random Quadratic Forms. Yale University, Department of Mathematics, New Haven, Connecticut, September 21-24, 1987.

Malley, J.: Jordan Algebras and Statistical Inference in Quantum Dynamics with Reference to Biologically Active Molecules. University of Massachusetts, Department of Mathematics, Amherst, Massachusetts, December 2-4, 1987.

Malley, J.: Jordan Algebras and Quantum Statistical Inference. University of Maryland, Baltimore Campus, Department of Mathematics, Catonsville, Maryland, February 8, 1988.

Malley, J.: Variance Component Estimation. Wright State University, Department of Statistics, Dayton, Ohio, October 30, 1987.

Malley, J.: Variance Component Estimation and Genetic Evaluation. Louisiana State University, Medical Center, Department of Biometry and Genetics, New Orleans, Louisiana, November 3-4, 1987.

Malley, J.: Variance Component Estimation and Genetic Heritability. University of North Dakota, Department of Animal and Range Science, Fargo, North Dakota, July 6-9, 1987.

Malley, J.: Variance Component Estimation in the General Linear Mixed Model. Oregon State University, Department of Statistics, Corvallis, Oregon, April 18-19, 1988.

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PSI

Physical Sciences Laboratory

George H. Weiss, Ph.D., Chief

Modern investigations in the biomedical sciences call for a sophisticated mixture of scientific disciplines that include, physics, mathematics and computer science in addition to the biological and chemical sciences. The Physical Sciences Laboratory (PSL) provides a mixture of scientists engaged in all these subjects, with emphasis on applications of physics in biology. PSL presently consists of six scientists with varied backgrounds, together with international visitors who work with members of the laboratory in a number of research projects. The work of the laboratory consists of theory and experiment, much of which is done in collaboration with scientists at other institutions both at NIH and universities.

An example of the experimental work of PSL is a study of membrane transport, in which osmotic stress techniques are used to measure volume change of potassium channels in the squid giant axon. This study is relevant to the transmission of information along nerve cells. The project involves a significant computer component as well as the development of new graphics systems which have potential application to many other types of experiments. Theoretical work done in PSL includes a continuing investigation of photon migration in turbid biological media. This is done in close collaboration with the Biomedical Engineering and Instrumentation Branch (BEIB) and has application to lasers used for a variety of medical purposes.

A project completed this year is a study of the effects of a pigmented layer on the surface of tissue being irradiated. It was shown that a measurement of the surface intensity as a function of distance from the point of radiation injection can provide information about the thickness of the layer. Other studies include the development of models for the gelation and elasticity properties of complex cytoskeletal networks, the continuing development of an approximation-free theory of crystallography, the solution of problems related to the optimization of NME measurements, and generalizations of the Smoluchowski theory for chemical reaction rates.

The efforts of PSL members are internationally recognized as evidenced by a number of editorships and presentations. For example, Dr. B.K. Lee was invited to speak at a meeting of the International Union of Pure and Applied Chemistry in Prague; Dr. V.A. Parsegian was an invited speaker at the International Meeting on Surface Interactions in Jerusalem, international meetings on Bioelectrochemistry in Budapest and the Physical Chemistry of Bilayers in Gottingen; and Dr. G.H. Weiss was an invited speaker at an international meeting on the Physics of Condensed Matter in Jerusalem.

Research Projects

Diffusion Controlled Reactions

Noam Agmon, Ph.D.

with: A. Szabo, Ph.D. (NIDDK/LCP); G.H. Weiss, Ph.D. (DCRT/PSL); R. Zwanzig (NIDDK/LCP).

Diffusion in a bounded potential with coordinate-dependent reactivity serves as a model for the effect of conformational change on ligand-binding to heme-proteins. The effect of increasing solvent viscosity on this biophysical process can be described mathematically as a decrease in the ratio of diffusion to reaction rates. We are investigating this effect by obtaining expansions for the survival probability (of the unligated heme) as a function of this ratio in the limits of large and small diffusion coefficients.

The Smoluchowski assumption of independent-pairs for describing the kinetics of (many-body) diffusion-controlled reactions is used extensively for analyzing fluorescence-quenching experiments in solution, but the range of validity for this approximation is unclear. We have analyzed the kinetics of an excited molecule in a random distribution of quenchers in one-dimension by obtaining the correction-term in the density expansion describing the short-time behavior of the survival probability of the excited-state molecule.

This analysis is based on our ability to understand the dynamics of three particles on the line. It provides both a correction to the Smoluchowski theory as well as an assessment of its validity.

Correlation Function Spectroscopy/Neutron and Light Scattering

Ralph J. Nossal, Ph.D.

with: Bonner, PhD. (DRS/BEIB); S.H. Chen, Ph.D. (Mass. Inst.Tech).; R. Gammon, Ph.D. (Univ. Maryland); S. Havlin, Ph.D. (Bar-Ilan Univ., Israel); J. Hofrichter, Ph.D. (NIADDK/LCP); J.E.Kiefer (DCRT/PSL); S. Krueger, Ph.D. (Nat. Bur. Standards); J.T. Russell, Ph.D. (NICHD/LNN); G.H. Weiss, Ph.D. (DCRT/PSL).

We have extended our theoretical studies of photon migration in turbid biological media (R. Bonner, S. Havlin, J.E. Kiefer, and G.H. Weiss). New work has included investigating light diffusion in layered tissues analyzed by using specially designed computer-based enumeration of probability densities of photons moving on a lattice. In addition to substantiating our earlier analytical work, results indicate that, when an underlying tissue layer has a lower absorption than the upper layer, photons re-emitted far from the point of insertion will move primarily within the underlying layer. We thus infer that the optical characteristics of the lower tissue layer in this case can be evaluated by examining surface emission at distances greater than L, where L is the thickness of the superficial layer. In contrast, when the lower layer is more highly absorbent than the superficial layer, the decrease in tissue properties causes an increased loss of photons with deeper trajectories. Photons that emerge at large distances predominantly sample the interface between the two layers. Other work has involved deriving mathematical expressions for distributions of the depths at which photons travel, which should be of assistance in assessing laser Doppler measurements of microvascular blood flow.

Facilities have been upgraded for performing quasielastic and dynamic light scattering studies (R. Gammon). These facilities have been used to examine the effects of salts and pH on the assembly of supramolecular structures formed by the peptide hormones within the neurosecretory vesicles of bovine pituitaries (S. Krueger and J. T. Russell). Other studies with this equipment have involved the use of dynamic light scattering to measure parameters pertaining to the response of transiently bonded gels. When a sample is subjected to externally imposed mechanical excitation, a resonance in the frequency dependence of the response is observed if the relaxation times for bond formation and breakage are long on a time scale determined by the dimensions and the instantaneous shear modulus of the sample. However, if the relaxation is fast on such a time scale, the response does not resonate and is maximal at zero frequency. The half-widths of spectral response are related to the internal restructuring of the gel matrix.

We also have continued studies on neutron scattering from dense biological media (S.H. Chen, J. Hofrichter and S. Krueger). In particular, differential crossections for neutrons scattered by human HbA have been analyzed over a wide concentration range, up to ca. 35 weight percent protein. Data have been compared with theoretical structure factors calculated from models of interacting spheroids to determine possible complex formation in highly concentrated solutions.

Biophysical Analysis

Ralph J. Nossal, Ph.D.

Additional studies of mathematical models relating to the gelation and elasticity of complex cytoskeletal networks have been conducted. The nature of the biological system requires development of time-dependent models. Mathematical expressions have been obtained for viscoelastic coefficients in terms of concentrations of network constituents and kinetic constants for crosslinking. The feasibility of using dynamic light scattering to measure elastic storage and loss moduli has been examined, and conditions necessary for resolving spectral data have been determined.

Interactive Molecular Graphics

Byungkook Lee

with: J. L. Syi, Ph.D. (DCRT/OD)

The development of menu-driven interactive molecular graphics software is in its third year. It is now a mature program and is especially easy for scientists without computer expertise to use. It is routinely used in the molecular graphics group. We have also received numerous requests for this program from all over the world.

The program presently runs only on the Silicon Graphics computer. The project goal for this year is to write a general interface routine so that the main portion of the program is machine independent. Once this is achieved, the program will be transportable to different machines with minimal adaptation. The immediate goal is to make it run on Apollo and the Stellar workstations.

Theoretical Study of Hydrophobicity

Byungkook Lee

with: J. L. Syi, Ph.D. (DCRT/OD)

Of all the forces that operate to keep a globular protein molecule in the globular shape, the hydrophobic force is considered to be the most important. Yet it is also the most poorly understood of all the forces.

Last year, reliable values were obtained for the enthalpy of solvent reorganization by combining the experimental data and computer simulation data at room temperature. The surprising finding was that the enthalpy change on reorganization of water molecules around an inert solute was positive, but smaller than the change for hydrocarbon liquids. These findings provided important clues to the origin of hydrophobicity. This year, the temperature dependence of the solvent reorganization process was studied using Baldwin's summary of experimental data and Gill's equation for the heat capacity change. Both the enthalpy and entropy changes of water reorganization are found to be strongly rising, but nearly compensating, functions of temperature. Thus the enthalpy change of water reorganization is not at all small at higher temperatures but the free energy change remains nearly constant with temperature.

This observation completes the overall outline of a picture of the physical mechanism of hydrophobicity. It is now clear that hydrophobicity is a result of the small size of water molecules. The "iceberg" formation, which has long been considered the mechanism of hydrophobicity, is actually a neutral process with a small hydrophilic contribution to the dissolution process.

Protein Folding
Byungkook Lee

with: J. L. Syi, Ph.D. (DCRT/OD)

Determination of the three-dimensional structure of a globular protein molecule from its amino acid sequence remains one of the major unsolved problems in biology. One of the crucial ingredients missing for a successful solution of this problem is the lack of understanding of the most important of the forces involved in the process, the hydrophobic effect. We feel that we have now achieved a clear understanding of this force. The other essential ingredient is a powerful computer. However, rapidly advancing computer technology makes a solution seem hopeful. We plan to start a study program to solve this problem.

The dynamic Monte Carlo technique being pioneered by Dr. Skolnick in St. Louis is being adopted to solve the problem. It will be modified to include rule-based generation of configurations. In the past year, an essential technical problem has been studied to use this technique for real protein molecules. The problem involves efficiently generating local perturbations of a protein molecule. Currently available algorithms take several seconds to generate each local perturbation, which is prohibitively slow. However, a slight, artificial modification in the geometry of the peptide group has been found to generate local perturbations efficiently.

In the coming year, we plan to write a computer program to test this procedure. This will start a protein folding study that will probably take several years to complete.

Molecular Forces in Cellular Assembly
V. Adrian Parsegian, Ph.D.

with: E.A. Evans, Ph.D. (Univ. of British Columbia); D.F. Evans, Ph.D. (Univ. of Minnesota); S.M. Gruner, Ph.D. (Princeton Univ., NJ); R. Podgornik (Lubljana, Yugoslavia and NIDDK); R.P. Rand (Brock Univ., Canada); D.C. Rau (NIDDK); J.J. Zimmerberg, M.D., Ph.D. (DCRT/PSL); J.J. Kasianowicz, Ph.D. (NIDDK) and E. Curtin (NIDDK).

Our ability to measure directly the forces between macromolecules or between membrane surfaces, developed over the past several years, has verified the idea that different properties of matter emerge to dominate behavior at different levels of size or complexity. The main features that emerge from these measurements are:

- in the important last few nanometers where molecules approach contact, interaction is dominated by the removal of water solvent from their surfaces; this became clear from the work with Professor Rand on forces between bilayers and later in measurements with Dr. Rau and Dr. B.K. Lee on forces between DNA double helices; it is also apparent from measurements made with Dr. Rau during the past year on forces between linear polysaccharides;
- at larger distances macromolecules or membranes move or undulate to repel by the "steric" action of molecules colliding. During the past year and a half, primarily through collaboration with Dr. Podgornik, it has been possible to simultaneously measure the motion of DNA double helices as well as the force between these molecules as they are brought together. A remarkable feature has emerged: it is the work of stretching out large molecules, rather than the straight energy of their interaction, that dominates the process of bringing macromolecules together, but that straightening out comes from the long-range intermolecular forces that prevent the molecules from touching.

Both these kinds of forces—that due to water solvation and that of macromolecular reconfiguration—can be expected to act inside a biological cell whose functioning units are assemblies of molecules or membranes in continuous and controlled reorganization.

The data derived from the osmotic stress technique as we have been developing it can be used in many ways.

One is to provide information for a more correct theoretical description of molecular interaction and assembly. For example, there is an interplay between force and motion such that as molecules are brought together there is a continuous change in the freedom, or entropy, of motion; there is in fact a mutual enhancement of the steric force of molecular freedom and the actual forces between molecules that cause each other to lose their freedom. Collaboration with Drs. Podgornik, Rau and E. Evans is now addressing the theoretical description of molecular motion in intermolecular force fields. This involves computer simulation as well as statistical mechanical analyses. It also involves comparing forces measured between molecules in solution and those between molecules that have been attached to surfaces which presumably limit motion (a nascent collaboration with Drs. D.F. Evans and R.P. Rand).

A second use of the data is to see how the measured forces act at the functional level of, for instance: controlling the contact and fusion of membranes as in a secretory process (addressed by Dr. Zimmerberg in a separate report); or determining the packing of DNA or other long molecules; or perturbing the rearrangements of protein structure that affect the "gating" of trans-membrane ionic channels (a current study with Drs. Kasianowicz and Zimmerberg on the voltage dependent anion channels from mitochondria); or lipid structure in the formation of non-lamellar aggregates (with Drs. Gruner and Rand); or even affect the activity of enzymes whose function depends on particular forms of packing components (a set of measurements with Drs. Rau and Zimmerberg and Ms. Curtin on aspartate transcarbamylate).

Third, we see the possibility to introduce measured force and motion information into molecular dynamics algorithms to bring the benefit of this information to the active but still relatively formal area of computer simulation. With Drs. Podgornik and Rau we are beginning a simulation study that we hope will later develop into a full-fledged effort with the DCRT Molecular Graphics and Simulation Lab.

Instrumental Analysis

George H. Weiss

with: J.A. Ferretti, Ph.D. (NHLBI); U. Shmueli, Ph.D. (Tel-Aviv University, Israel); J.E. Kiefer (DCRT/PSL).

The two major projects include the analysis of error in and optimization of NMR experiments, and the development of an exact theory for the calculation of probability densities for analysis of crystallographic data.

The first part of a project on the optimal choice of apodization functions for data reduction in FT-NMR has been completed. This effort is designed to reduce bias and fluctuations as far as possible. Spectrometer manufacturers offer a limited choice of apodization functions but they have not proved to be optimal. This study has explored the range of parameters required for the specification of these functions as well as extending the functional form of apodization functions that may be used.

In the area of crystallography we have completed a calculation of the probability density function for the three-phase invariant in space group P1. This involves a very complicated use of symmetries to reduce the computer running time in the evaluation of the six-dimensional Fourier representation. Earlier attempts to evaluate such series without taking symmetries into account proved fruitless even on a supercomputer. Investigation results agree with qualitative results obtained in earlier calculations of direct methods of phase determination that the approximate techniques in current use are too conservative. This error can be as high as 100 percent in the presence of atomic heterogeneity.

A second project relates to the effects of anomalous scatterers on the probability density function for the scattering intensity. Theory results show that the major effect of anomalous scattering appears at low intensities. In this case, the necessary theory on complex scattering factors required the development of new mathematical techniques for calculating the probability density. These techniques are now being applied to a variety of other problems in crystallographic analysis with a related mathematical structure.

Studies in Mathematics and Statistics

George H. Weiss, Ph.D.

with: (DCRT/PSL) S. Havlin, Ph.D. (Bar-Ilan Univ., Israel); J.E. Kiefer; N. Agmon (DCRT/PSL); J.T. Bendler (General Electric, Schenectady); H. Weissman (Bar-Ilan Univ., Israel); H. Kesten (Cornell Univ.); R. Kopelman, Ph.D. (Univ. of Michigan); A. Szabo, Ph.D. (NIDDK); M. Dishon, Ph.D. (NBS).

The two major themes in this study involve transport in disordered media and the development of models for reaction kinetics in chemistry. In addition, research was done on the calculation of the dependence of the relaxation time for the transition from elastic viscosity to plastic viscosity behavior of a polymer on the molecular weight.

Together with S. Havlin and R. Kopelman we have investigated the spatial distribution of reactants in one and three dimensions. In one dimension the kinetic properties do not follow classical laws while in three dimensions they do. We show that these effects are due in part to the non-Poisson spatial distribution of reactants in one dimension.

Measurements of the dependence of the relaxation time polymer viscosity on the molecular weight deviate from the theoretical prediction that such dependence should go as the inverse third power. Experiments are consistent with the dependence on a power that ranges between −3.3 and −4. Together with J. Bendler, M. Dishon and H. Kesten a physical model has been produced in which the indicated power is −10/3 which is more consistent with the experimental data than earlier theoretical work.

Membrane Transport

Joshua Zimmerberg, M.D., Ph.D.; V.A. Parsegian, Ph.D.

with: F. Bezanilla, Ph.D. (UCLA, CA); A. Harris, Ph.D. (J. Hopkins, MD); A. Walter, Ph.D. (Wright State, OH); S. Lesher (DCRT/PSL) and J. Kascianowicz, Ph.D. (NIDDK/LBM)

Information is transmitted along nerve cells by the controlled opening and closing of protein channels in the nerve membrane. We have applied our technique of osmotic stress to the squid giant axon to measure the change in volume of the potassium channels. About 20 molecules of water appear to enter the average channel when it opens. We postulate a number of closed states under voltage control and a final opening state that is voltage-independent but osmotically sensitive.

Toward a more detailed study of protein channels in planar bilayers of defined lipid environment, a PC computer software/hardware combination is being developed to accurately measure equilibrium statistics of channel conformation. To date, our systems allow for continuous acquisition to disk at 11 microseconds per 15 bit point, and automatic determination of the open/closed times. We are currently interfacing the computer to the experimental setups, to allow closed-loop voltage control as well.

New techniques for membrane channel purification and incorporation into planar lipid membranes have been used to study the gap junction of the rat liver (connexin32). Isolated vesicles permeable to sucrose which contained junctional material were isolated. When fused to bilayers, these vesicles induced channel activity with three major conductance levels (20, 50 and 150 pS), were asymmetrically voltage-dependent and somewhat anion selective. Western blotting techniques quantitatively confirmed the presence of connexin32 in the shifted vesicles in amounts more than sufficient to mediate the shift.

Cell Membrane Fusion Studies

Joshua Zimmerberg, M.D., Ph.D.

with: D. Chandler, Ph.D. (Arizona State, AZ); F.S. Cohen, Ph.D. (Rush Medical College, IL); M. Curran, Ph.D. (NIDDK/LBM); A. Marty, Ph.D. (Ecole Normale Superieure, France); S.J. Morris, Ph.D., and R. Blumenthal, Ph.D. (NCI/LTB).

Membrane fusion is a ubiquitous phenomenon underlying hormonal release, neurotransmitter discharge, sperm-egg union, muscle development and enveloped viral infection. Last year we discovered that in the beige mouse mast cell biological membrane fusion is initiated by a small, hydrated pore, in contrast to lipid membrane fusion which is characterized by a rapid, large rupture of a pre-fusion septum. We have since measured, in the beige mouse mast cell, the time course of 350 exocytotic events, and made over 42,000 independent determinations of pore conductance as a measure of the size of the initial pores. We have also searched rapidly-frozen mast cells with electron microscopy and found a class of small initial pores. The occurrence probability for pore conductance is maximal for pores between 1 and 4 nanosiemens, with a second maximum for larger pores which may correspond to the electron micrographs. No quantized changes are seen, and the size, time-course and reversibility of these small exocytotic pores is richly variable. We conclude that the fusion pore in the beige mouse cell is initially smaller than the smallest pores seen in the electron microscope, and of a size where hydration forces predominate. It then grows to larger sizes, still comprising an aqueous pathway for ion movement. However, it is fundamentally different from pores hitherto detected composed of lipid or protein alone.

Fusion measurements have begun in a system with identified fusion proteins—the influenza virus. Digital computer imaging has been used to study the transfer of fluorescent dye from red blood cells to NIH 3T3 cells expressing the viral fusion protein HA. Dye transfer has been documented in lipid/lipid exchange and cytophasmic marker exchange. Establishment of the temporal sequence of events during membrane fusion is planned. By combining digitally processed, dual-wavelength fluorescence, transmission and differential interference contrast microscopy together with whole-cell current and capacitance measurements, simultaneous measurements of diffusion of lipid dye, initial pore formation, release of soluble dye pore, the widening of the pore with time and the release of hemaglobin can be obtained.

The membrane fusion during exocytotic secretion from exocrine glands is triggered by muscarinic activation. We have been studying this activation directly, using the release of calcium which is the intracellular messenger for fusion. This is normally stimulated by acetylcholine from parasympathetic neurons. Secretion from exocrine glands is also stimulated by acetylcholine released from parasympathetic neurons. It was shown that a rundown in activation occurs during intracellular perfusion, and that the rundown is due to the loss of a water soluble cytoplasmic compound necessary to the muscarinic response. Thus we can equate rundown and washout. It was successfully determined at what point along the chain of events leading from receptor occupancy to channel activation the compound is acting by adding second messengers to depleted cells via a second patch pipette. Results indicate that a 300-500 molecular weight solute is likely to be an unknown cofactor of Gp, the GTP binding protein linked to phospholipase C.

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CSL

Computer Systems Laboratory

Alan M. Demmerle, Chief

The Computer Systems Laboratory works closely with other divisions and institutes to apply state-of-the-art computer hardware and software technology, particularly in the areas of communications, laboratory automation, image processing and expert systems, to the biomedical and clinical research programs of NIH. CSL's staff of 28 includes engineers, computer scientists and mathematicians.

CSL is currently engaged in 22 projects that cover a wide variety of applications and range in effort from several man-months to tens of man-years. Most projects involve identifying, purchasing and integrating commercially available hardware and software and adapting it to a particular application. This usually requires some software development, and occasionally the design and building of custom hardware to connect a computer to laboratory instrumentation. These projects require:

- familiarity with the rapidly changing computer hardware and software marketplace to enable selection and purchase appropriate products;
- a deep understanding of computer technology to resolve the inevitable problems associated with design of individual components into a complex system;
- and a background in biology, medicine, chemistry or physics to communicate with collaborating NIH researchers.

The Laboratory initiates projects when a new computer technology emerges that can potentially benefit the NIH community of researchers at large. Prime examples include the NIH Campus Area Network Backbone and the Advanced Laboratory Workstation Projects.

Requests for help from other institutes or divisions with a particular laboratory computer problem motivate the other CSL projects. These involve collaborating with scientists who will be using the particular system. Although CSL usually builds systems, advice is also offered when requested by intramural programs, extramural programs, other agencies or non-government centers.

Because of limited personnel resources, CSL continues to emphasize projects that have the widest possible impact on biomedical research at NIH.

Networks and Laboratory Workstations Highlight FY88

Three closely related networking projects, the DCRT Local Area Network Project, the NIH Campus Area Network Project and the Advanced Laboratory Workstation Project, together occupy about one-half of CSL's staff and two-thirds of its budget, indicating the importance placed on these activities. This section highlights these projects; details on all of CSL's projects are in the *Research Projects* section.

The personal computer (PC) revolution that began five years ago has resulted in the installation of about 5000 PC's at NIH. These machines are popular because they are economical, easy to use, flexible and responsive. PC's have their drawbacks, however:

- Enabling PC users to communicate easily with one another the way mainframe users are accustomed to is difficult, particularly when large numbers of machines must be interconnected. Individual branches, laboratories and institutes, including DCRT, have installed a variety of networks to meet their particular needs, but about 4000 PC's are still unconnected.
- Although PC's place computing power directly in the hands of the user, they also burden him/her with the responsibility of administration: recognizing and reporting problems, installing software, updating documentation, backing up disk files and purchasing new equipment to meet growing needs.
- PC's offer a rather limited range of computing power (about 1-3 MIPS). At a diverse organization such as NIH, PC's cannot solve all problems for all computer users. Many users still need access to more powerful workstations, minicomputers, mainframes and supercomputers.

CSL is vigorously pursuing the DCRT Local Area Network, NIH Campus Area Network Backbone and Advanced Laboratory Workstation projects as a solution to these problems.

The DCRT Local Area Network

CSL designed and installed the DCRT Local Area Network, a thick-wire Ethernet, in FY84. Today, this network has grown to support over 140 PC's and workstations located in Buildings 12, 12A, and 12B. Forty nodes were added to the network in FY88.

The DCRT Local Area Network serves several purposes. Designing, installing and maintaining a network of this size has provided valuable experience which is passed on to other organizations at NIH who need expert advice. CSL's NIH Campus Area Network and Advanced Laboratory Workstation Projects and several other branches of DCRT utilize the network as a testbed for research and development. But mostly, DCRT staff members rely on the network for daily production use, particularly the electronic mail and laser printing services it supports—it has become as essential as the telephone for most of its users. In the future, because of its strategic location, it will become the home of many services to be distributed NIH-wide via the NIH Campus Area Network.

The NIH Campus Area Network Backbone

CSL began developing the NIH Campus Area Network Backbone in FY85 as a means of interconnecting the Local Area Networks (LAN's) to be located in 32 buildings at NIH. In FY88, construction began on inter-building conduit paths and inter-floor riser systems within buildings, and installation of cable began. This work is estimated to be completed in the first quarter of FY91. Initially, the campus backbone will employ broadband coaxial cable technology with a data rate of five megabits per second per channel. Later, it will be converted to fiber optic technology with a data rate of 100 megabits per second.

LAN's will connect to the campus backbone through Network Interface Units. A wide variety of commercial products are being evaluated for this purpose, and we expect to complete this evaluation and arrive at a decision in FY89.

Work also began this year on another important aspect of the NIH Campus Backbone: devising a method of monitoring network activity to assure reliability and the ability to quickly locate and resolve problems.

The Advanced Laboratory Workstation Project

CSL is exploring the uses of 32-bit UNIX workstations on the network the laboratory is building at NIH. Efforts are being concentrated on the UNIX operating system as a potential solution to problems presented by PC's, including software installation and connectivity.

CSL is working in close collaboration with the Computer Center Branch's Laboratory Systems Unit on this project. Efforts are focused on three areas: the distributed file system, the network-transparent window system and application toolkits.

The distributed file system software creates the illusion of a single, large, shared file system that can be accessed by UNIX workstations and IBM PC's attached to the network, and is thus the cornerstone of the project. In reality, files are stored on dedicated file server machines that are also connected to the network and distributed across the NIH campus. This year, the Andrew File System (AFS) has been tested on some workstations. AFS is unique in that its developers at Carnegie-Mellon University (C-MU) designed it to handle large scale networks connecting thousands of workstations. Our experience with AFS has been good, but limited due to a critical shortage of disk space. Procurement problems have delayed the purchase of an additional file server, seriously hampering the progress of the project.

Disk space shortage should be alleviated by early FY89 so that AFS can be fully deployed on all workstations at DCRT and NIDDK's pilot network in Building 2. Ten file servers will also be deployed in FY90, when a major portion of the NIH Campus Area Network will become operational. Each file server will store approximately three gigabytes of data.

The network-transparent window system enables workstation users to interact graphically with several programs at once. The term "network-transparent" means that these programs may reside in any machine connected to the network, even those machines manufactured by different vendors.

Application toolkits are software packages used to build the user interface to application programs, and give the computer system its "look and feel." Technology in this area is still emerging, and several competing approaches are being evaluated. The most advanced toolkit is the Andrew Toolkit, developed at Carnegie-Mellon University. It employs object-oriented programming (OOP) techniques and supports sophisticated multi-media applications, such as an editor and mailer that can handle text, drawings, equations, spreadsheets, raster images and simple animations. Work this year has concentrated on a version that has many flaws and lacks some fundamental features, but may be extended to handle objects that would be particularly useful to NIH researchers, such as plots of scientific data, protein sequences, chemical structures and molecular models.

Computers in Cardiology

CSL continued its support of the annual international conference, Computers in Cardiology. The conference, which was held in Bethesda, Maryland this year, was jointly sponsored by DCRT, NHLBI and CC. Individuals from the three organizations comprised the local committee which planned the program and organized the meeting.

The conference brought together physicians, computer scientists and engineers in a common forum to focus on the progress and problems in applying computer technology to clinical cardiology and cardiovascular research.

Two new components were introduced this year. An invited session was presented which highlighted NHLBI research in areas related to this conference. Another new aspect which we hope will continue as part of the conference was an industry forum. A specific new technology area was selected and manufacturers were invited to present scientific papers about their product. This year's Industry Forum focused on realtime solid-state ambulatory ECG arrhythmia monitors.

Future Plans

CSL expects no major shift in emphasis or type of work next year. Most of the projects reported here will continue into the future. However, some emerging technologies with application to NIH research are or will be investigated. These include:

- fiber optic communications, which will increase the speed of local and campus area networks to at least 100 megabits per second—speed needed to accommodate transmission of high-resolution images;
- optical storage technology, which promises solutions to the problems of backing up and archiving large volumes of data, and of economically distributing large static databases, such as protein sequence data;
- network-accessible databases, to give thousands of PC's and workstations rapid access to centrally-maintained databases; and,
- highly parallel computing systems, including uniprocessors with multiple functional units and vector hardware, processor arrays, shared-memory multiprocessor systems, distributed memory multicomputers and neural networks.

Research Projects

Advanced Laboratory Workstation

K. Gorlen

with: P. Plexico, J. Powell, R. Dew, J. Sullivan (DCRT/CSL); J. Dickson, S. Fellini, A. Salemme, J. Small (DCRT/CCB).

The Computer Systems Laboratory and the Laboratory Systems Unit of the Computer Center Branch are working together to provide researchers with 32-bit, UNIX-based, high-performance workstations manufactured by a variety of vendors. The workstations will be interconnected by the NIH campus-wide network, by which they will share resources and access services such as file backup, software maintenance, online documentation, nation-wide electronic mail and news, computation and database servers and laser printers. Potential applications for Advanced Laboratory Workstations (ALW's) include interactive graphics, laboratory data acquisition and analysis, modeling, image processing and desktop publishing. We are adapting software from similar projects which have been underway for several years at Carnegie-Mellon University (Project Andrew) and at the Massachusetts Institute of Technology (Project Athena).

Among the activities of the ALW project this year:

- We succeeded in obtaining software licensing agreements for all critical software components: AT&T UNIX System V, Berkeley 4.3 UNIX, IBM Academic Operating System, Sun OS, and DEC Ultrix.
- We increased the number of client workstations in use on the project in DCRT to a total of nine Sun-3's, seven IBM RT's, and two DEC VS2000's. A Sun-3/180S and an IBM RT act as file servers for these workstations. In NIDDK, a Sun-3/180S acts as a file server for four Sun-3s and one MicroVAX II.
- A T1 link now connects the DCRT Ethernet to NIDDK's Ethernet in Building 2, enabling workstations on either network to transparently access files, open X window connections or use laser printers on the other network.
- We installed domain name server software on an ALW, which translates host names to Internet addresses for all computers using the TCP/IP protocol suite that are attached to either the DCRT or NIDDK Ethernets. In conjunction with DCRT's connection to the SURANET via the University of Maryland, we can now perform remote login and file transfers to over 20,000 hosts connected to the Internet.
- The Andrew File System (AFS, previously called VICE) has been installed and is being used on the IBM RT's and two of the Sun-3's. Using C++, we have developed a working version of software to manage centralized backup of Andrew file servers over the network, but we have been unable to install AFS on all workstations or fully exercise the backup software due to lack of storage.
- Version 11 of the X Window System on all workstations has been installed and is in use.
- The Andrew Tool Kit and applications, particularly the multimedia editor has been installed and is in use.

- We obtained a Sun-3/50 workstation for LSM, which was used to evaluate the S statistics package. We also obtained the SPSS-X statistics package and MACSYMA, a symbolic algebra system for LSM to evaluate. The software has not been installed due to a shortage of disk space.
- Work continued with C++ and development of the Object-Oriented Program Support (OOPS) library, in order to prepare a course and write a book describing this software.

Next fiscal year will see sufficient progress in the areas of distributed file systems and applications software to determine the success of the pilot ALW network. Support is planned for at least two additional workstation models: the Sun 386i, based on the Intel 80386 microprocessor, and the Sun-4, which uses Sun's Scalable Processor Architecture (SPARC). In the area of communications, the multi-media mailer will be made to work on all workstations.

NIH Campus Wide Network Backbone

R. Fico

with: H. Ostrow, L. Freeman, M. Shaffer, J. Kabara, E. Suh, and T. Kuhfuss (DCRT/CSL).

Starting in FY85, CSL began developing a Campus Wide Network to interconnect local area networks (LAN's) campus-wide. This interconnection will occur via a state-of-the-art communications system called a backbone. Connection to the backbone will be simple.

The backbone consists of a cable system and network interface units for connecting independently managed local area networks. The cable system uses two technologies: broadband coax and fiber optics. The broadband coaxial technology is very mature. Supported by the commercial market, it will be used in the early years as the production system. Fiber optic networking technology is in a state of change with developing standards, decreasing prices and improving products. CSL has decided to wait for the fiber technology to settle down before using it.

A major effort involved in installing the backbone system is the physical construction required to modify buildings, create underground conduit paths between buildings and install cable.

The Division of Engineering Services of the Office of Research Services is helping CSL with this aspect of the backbone system. Modification within buildings includes the construction of closets to house the cable system electronics and network interface units for network security by restricting physical access. Most buildings will have one or two interbuilding closets to connect to the backbone system; however, the tall buildings (10, 31, 36 and 37) will have vertical stacks of closets, called risers, to access the backbone system. In FY88, a schedule for backbone implementation was completed and is shown in Table 1. This schedule represents the estimated times expected to complete a fully functioning cable system in each building.

In FY88, the physical work for interconnecting Buildings 12A, 13, 29 and 10 was completed. Also in FY88, the construction of the Building 31 riser system began and the riser plans for Buildings 10, 36 and 37 were started. Research into a network monitoring system began in FY88, and in-house development using dBASEIII+ with plans to migrate to dBASEIV was started.

In FY89, CSL and DES will continue to work toward meeting their schedule and CSL will begin installing cable system electronics via contract. Also in FY89, we expect to arrive at network interface solutions. Implementing the backbone cable system is the first step toward achieving high-speed communication on the NIH campus. Once the cable system is in place, network interface units will connect BID LAN's to the cable system to complete, thereby completing the backbone "picture."

Recently, a number of network interface products have become available. These units are known in the industry as bridges and routers, each with distinct characteristics of performance, support of different network protocols and connection to various cable technologies. CSL is actively investigating best approaches to using these devices for best performance and lowest cost of cable system connection. Once the network becomes

Table 1.
NIH Campus Network Backbone Implementation Schedule

	FY89	*FY90*	*FY91*
12A, 13, 29	2nd qtr		
29A, 30	3rd qtr		
36, 37		2nd qtr	
1, 3, 5, 8, 12, 16A, 38		3rd qtr	
2, 4, 6, 15K, 20, 31, 60, 10		4th qtr	
7, 9, 21			2nd qtr
11, 14A, 28, 32, 41			3rd qtr

operational, monitoring activities will increase the reliability of the network. Such activities include inventory, maintenance, installation and modification tracking and data flow collection accompanied by traffic analysis.

Research into a network monitoring system began in FY88. The network monitoring project will continue in FY89 with continued development and market research. If needs are met by a commercial product, that product will be incorporated into our monitoring procedures.

DCRT Local Area Network (LAN)

R. Fico

with: L. Freeman, M. Shaffer, T. Kuhfuss (DCRT/CSL).

To develop expertise in LAN technology, and provide interconnection of personal computers, terminals, modems and computer systems, CSL installed an Ethernet network to serve DCRT. Ethernet was selected because of its status as an established standard and its support from a broad spectrum of companies. CSL Ethernet network, with eight connections (nodes), was designed and installed in FY84, and was extended to other parts of DCRT in Buildings 12 and 12B in FY85. The network has been growing steadily. This year 40 nodes were added, bringing the total to 180.

Four years later, the DCRT network is heavily used for inter-office communication/terminal-to-host communication, new product evaluation, systems development and administrative functions. It now supports eight file servers and 15 terminal servers.

In FY85, CSL installed a broadband coaxial system to connect the DCRT Ethernet with the Ethernet in Building 13. Baseband to broadband "gateways" allowed terminal-to-host (DECsystem-10) connections between these networks. These gateway devices were upgraded to bridges in FY87. As a result of this upgrade, many different types of protocols (e.g., XNS, TCP/IP, DECnet) can now communicate over this link. The significance of this is that Digital Equipment Corporation (DEC) computers using DECNet, 3Com local office area network equipment using XNS and powerful workstations using TCP/IP can communicate within their systems over this link.

CSL keeps abreast of network developments and remains active in evaluating promising techniques. In FY87, evaluation began on products that interconnect Token Ring systems to Ethernet systems.

Two product evaluations that are promising solutions to interfacing Token Ring networks to the Campus Wide Backbone began in FY88. The solutions include the 3COM 3+ Token Ring-to-Ethernet server as one test and a Proteon Router connecting two Ethernet 3+ networks as another test. The Computer Center Branch of DCRT plays a key role in the Proteon Router test.

An Ethernet over Twisted pair product known as LATTISNET manufactured by Synoptics was also evaluated. Evaluation included testing by CSL engineers. This product has gained much attention in the trade press and may be an excellent means of wiring within new buildings on the campus.

Efforts in FY89 will include evaluating alternative methods of interconnecting LAN's campus-wide by using the DCRT Ethernet as a base for experimentation. Tests will include routing and bridging products that may serve as network-interface-units between BID LAN's and the NIH campus backbone.

This year, CSL continued formal network management procedures. As part of this effort, CSL is developing a database pertinent to network management. This database includes information on network configuration, installation requests, quality assurance tests and remedial maintenance. CSL has also been using a network monitor to collect statistics of network activity and problems. This information is logged on a regular basis. It has been particularly useful in uncovering problems during installation of network equipment.

Auditory Brainstem Response (ABR) Analysis and Interpretation Expert System

J.M. Deleo

with: A. Pikus, D.A. Sklare (NINCDS).

This project is designed to build an expert system to analyze and interpret the Auditory Brainstem Response (ABR), an electrophysiological response of the brainstem to acoustic stimuli. Expert reading of the ABR is essential in clinical decisions concerning retrocochlear disorders.

A peak detection algorithm and a diagnostic inferencing knowledge base have been developed. This year, the knowledge base has been expanded considerably to include knowledge from several experts. This knowledge base has been implemented in an IBM PC/AT using the commercial shell, GURU. The rules that comprise the diagnostic inferencing knowledge base relate clusters of ABR features such as wave presence, morphology, latency and inter-peak latency to possible auditory brainstem lesion, multiple sclerosis, etc. As efforts to enhance and expand the knowledge base progressed, it became desirable to refine normal ABR latency limits in audiometrically defined sensorineural hearing. To resolve this, a methodology to predict ABR latency from audiometric contour was attempted, but did not produce conclusive results.

The system is expected to be evaluated in the Clinical Center. A paper detailing the project is also planned.

Flow Cytometry Advanced Data Analysis

L. Barden

with: R. Tate (DCRT/CSL); S. Sharrow (NCI/DCBD/IB)

The Flow Cytometry Advanced Data Analysis project is developing a computer facility dedicated to in-depth analysis of multi-parameter flow cytometry data. This facility will allow the implementation of a number of complementary analytical techniques, such as non-hierarchical cluster analysis using standard data formats and a standard graphics protocol controlled by a common user interface.

During FY88, CSL has implemented and documented a command-driven user interface and has made significant progress toward implementing an initial version of nonhierarchical cluster analysis using this interface. In addition, hardware has been purchased to allow a high speed network connection between the development system in CSL and the beta-test system which will be installed in NCI.

The Laboratory Analysis Program, a histogram analysis package developed for the Advanced Laboratory Workstation project, is now being converted to run in the ADAFC environment. In addition, work is underway to provide a high-speed data link to the NIH central computer facility's vector processor.

Hypertension Expert System

S.I. Allen, M.D.

with: H.R. Keiser, M.D. (NHLBI/IR-OD).

This year work began on an expert database system to assist NLBI staff physicians in selecting and modifying drug treatment schedules for hypertensive patients. It will provide staff with rapid and concise information on current and proposed tests, procedures and treatments. Such information is critical in designing efficient, cost-effective therapy plans which encourage long-term patient compliance.

In the first months of this project, computer programs were developed to store and retrieve available pharmaceutical products, adverse reactions and drug-drug interactions in a dBASE III system. All such programs run on a personal computer (PC) which is also used as a (MIS) Medical Information System terminal to the Clinical Center's patient data bank.

The pilot studies with H.R. Keiser, Chief, Hypertension-Endocrine Branch, involve designing and evaluating explicit queries of the computer database for use by clinic staff. As more experience is obtained, automatic queries and checking will be built into a program for use during doctor-patient encounters.

Future plans include formalizing rules and algorithms to optimize patient workups and drug dose titrations, constructing a drug usage history program to acquire and save patient data and improving the PC linkage and data exchange facility with the Clinical Center's Medical Information System.

Personal Computer-based Spectrophotometer Data Station

R. Tate

with: A. Schultz, Jr. (DCRT/CSL), and W.F. Hagins, Jr. (NIDDK/LCP).

Although older spectrophotometers do not have the sophisticated digital data acquisition and processing facilities that newer instruments have, they are often of superior optical design. They frequently are not used because they do not have a convenient user interface nor do they provide data output in digital form suitable for further computer processing. CSL and LCP have upgraded a Cary Model 14 Spectrophotometer by adding a modern solid-state electronics package, a digital wavelength readout and an analog-to-digital conversion system based on an IBM PC/XT. Software, written in Turbo Pascal and using a commercially available scientific and graphics subroutine package, handles data acquisition and provides some basic data manipulation capabilities. The data file formats are compatible with the Laboratory Data Acquisition Computer System (LDACS) format as well as the JCAMP format used by commercial spectrophotometric data display and analysis packages such as Spectra Calc. An Ethernet connection permits the transfer of data to other computers for further analysis, display or printing.

Expert Advisor for Shock Treatment

D. Syed

with: K.M. Kempner, H. Fredrickson (DCRT/CSL); J.E. Parrillo, M.D., M.A. Mazer, M.D., G.L. Akin (CC/CCM).

This project was previously reported under Expert Systems in Medicine. Expert systems represent an extension of artificial intelligence techniques and contain knowledge contributed by experts.

They function best in specific, narrowly defined, complex problem areas. A very important characteristic of these systems is that decisions and recommendations are explained and justified to the user. An objective for this project is to develop, in collaboration with the Critical Care Medicine Department of the Clinical Center, an Expert Advisor for Shock Treatment (EAST) for use in an Intensive Care Unit. The drug administration protocol includes the capability for long-term dose maintenance and eventual dose tapering.

Personal computer-based technology (IBM PC/XT or PC/AT) has been utilized in conjunction with an original generated BASIC forward-chained inference mechanism.

A knowledge base of approximately 1400 intervention-specific was originally developed, but has been supplanted by a revised set that does not explicitly reference interventions (drugs and devices) and is therefore much more adaptable to general treatment concepts. By implementing a table driven mechanism, and utilizing rule iteration, a greatly expanded knowledge base has been encapsulated in 900 rules. Numerous additions to the explanation, debugging and user interface capabilities of the inference mechanism are continually being added.

The successful implementation of expert systems technology in dynamic medical problem areas can lead to the design of more sophisticated research protocols. Expert systems will effectively allow the researcher to be continually present during the execution of long protocols, and to modify, within protocol limits, the necessary medical interventions in realtime.

Clinical testing of the prototype system began in FY88. Additional diagnosis-specific treatment rules, rules for drug tapers, and rules for blood gas and respiratory protocols are being developed. Design of increasingly sophisticated trend and expected drug response functions, online system implementation, integration of deep knowledge from drug models and knowledge refinement through performance assessment, constitute the major future goals.

Neuromagnetometer Computer System

R.L. Martino, Ph.D.

with: J.E. Sullivan (DCRT/CSL); S. Sato, M.D., D.F. Rose, M.D., D.S. Geduldig, Ph.D., E. Ducla-Soares, Ph.D. (NINCDS/Off. of Clin. Dir.); P.D. Smith, Ph.D., W.S. Friauf (DRS/BEIB).

The Medical Neurology Branch, NINCDS, the Biomedical Engineering and Instrumentation Branch, DRS, and the Computer Systems Laboratory, DCRT, are collaborating on a research project to noninvasively localize epileptic discharge sources within the human brain by using neuromagnetic recording in conjunction with conventional electroencephalogram (EEG) recording.

Many patients with seizure disorders exhibit low-level cellular discharges between seizures, indicated by interictal spikes or sharp waves in their EEG and magnetoencephalogram (MEG) recordings. This project involves the development of computer techniques for automating and enhancing the procedure that is presently used by NINCDS neurologists to determine the intracranial locations of the sources of epileptiform discharges in patients with epilepsy.

During the past year an algorithm was developed that automatically detects the epileptiform discharges from the EEG and MEG signals and tested with signals obtained from epileptic patients. This algorithm uses the weighted sum of the absolute values of the first and second derivatives of the signal as a measure of waveform sharpness. This measure is compared with a variable threshold to determine the occurrence of spikes or sharp waves. Three-dimensional displays of the outline of the patient's head were also developed showing where the magnetometer had been positioned during previous measurement sessions so that the neurologists can plan sensor positions for future sessions. A Signal Processing Workstation was added to the system and will be used in the future to perform various signal processing tasks.

In the coming year, the detection program will be tested with more patient data and implemented on the workstation to perform realtime detection. Methods will be developed for classifying the detected epileptiform discharges into types based on their morphology using correlation techniques. Anatomical data obtained from CT and MRI scans will be integrated with the three-dimensional displays of the outline of the patient's head so that epileptic sources can be represented relative to actual brain anatomy.

Image Processing of Electron Micrographs

B.L. Trus, Ph.D.

with: A.C. Steven, Ph.D. (NIAMS/LPB); P.M. Steinert, Ph.D. (NCI/DB); M. Unser, Ph.D. (DRS/BEIB), R.J. Podolsky, Ph.D. (NIAMS/LPB).

This project facilitates structure determination from electron microscopy. Suitable software, hardware and scientific expertise has been provided to allow other scientists, primarily at NIH, to use image processing and computer reconstruction to determine or understand a specimen's structure. Types of data analyzed include intermediate filaments, thin sections of both frozen hydrated myofilament of skeletal muscle and conventional stained embedded muscle, and liver coated vesicles. In addition, we are developing new computer algorithms to unwarp images, calculate factorial maps, perform image classification and determine mass densities for irregularly shaped particles.

The micrographs were taken with a Philips EM400T microscope and the Brookhaven STEM. Some micrographs were preselected by optical diffraction. Negatives were digitized on a Perkin-Elmer 1010MG microdensitometer and analyzed by means of the PIC computer system. Results were photowritten on the Perkin-Elmer microdensitometer or on a Matrix camera station. Images were processed using software developed primarily at NIH.

A major effort this year has been in the analysis of the cell wall of Bortedella Pertussis. It is composed of a 40K porin trimer. We have analyzed conventional transmission electron micrographs of muscle for comparison with our earlier frozen hydrated analysis. Substantial new software continues to be developed to correct for compression of the myofilament lattice as a result of the sectioning process as well as to correct other difficulties. This year's method, which improves over our previous methods, has been submitted for publication.

The results of our analysis are being evaluated. Additional effort has also been made in developing new software for the automatic processing of irregularly shaped two-dimensional STEM data.

Computer analysis of electron micrographs is still a relatively recent addition to the tools available to scientists for structural analysis. Few laboratories have the combined software and hardware capability to perform the image processing and image reconstruction available at NIH. These techniques are especially powerful when applied to two-dimensional crystalline structures. In addition, we can correlate and align similar particles that are not crystalline, and correct for a number of artifacts and experimental problems.

Software development will continue as needed. We have begun processing some 3-D images but continue to acquire or develop needed software. In addition, as new biological structures become available for analysis, these will be examined.

Molecular Graphics, Computer Modeling and Sequence Analysis

B.L. Trus, Ph.D.

with: A.C. Steven, Ph.D. (NIAMS/LPB); P.M. Steinert, Ph.D. (NCI/DB); B.N. Manjula, Ph.D. (Rockefeller University); S. Havlin, Ph.D., G. Weiss, Ph.D. (DCRT/PSL); B. Fraser (FIC).

The sequence of some regular proteins, when correlated with other structural information, such as data from x-ray diffraction, fiber diffraction, electron microscopy and spectroscopic analysis, can be used to evaluate models of protein or polymer structure. Four current studies involve the sequence analysis of keratin and other intermediate filaments (with NIAMS, NCI); sequence analysis of streptococcal proteins (with Rockefeller University); computer models of biopolymers (with PSL, DCRT); and analysis of protein sequences from viruses and bacteria (with NIAMS, FIC).

As the complete sequence of keratin, other intermediate filaments, and other helical proteins becomes available, an analysis of the sequence can proceed by studying periodicities in the sequence, and by computer prediction of the conformational properties of the specific amino acids in local regions of the chain. These predictions can be used to generalize structures where related sequences are available, and to draw conclusions as to similarities and differences.

Standard Fourier methods have been used to analyze the sequences and to cross-correlate sequences. These sequence regularities are usually correlated with structural features, such as the collagen triple helix, the alpha helix or the tropomyosin double stranded alpha helix. Using the computer methods of Chow and Easman or Robson one can predict other types of conformations (e.g., B sheet, coiled, turn). Additional software has been developed at NIH to illustrate correlations, to create maps of the linear sequences studied and to view inter- and intra-chain homologies.

This research is significant because many proteins do not form three-dimensional crystalline solids whose structure can be analyzed by classical x-ray diffraction. However, if these proteins are regular, comparison and analogy with related proteins can be used to model the unknown structures in order to understand the structure and functioning of the proteins. In addition, one can use computer models to analyze possible protein structures based on criterion other than regular periodicities.

This year computer models continue to be useful in studying biopolymers. Analysis of a new streptococcal M protein sequence and two mutants is in progress. We have also begun to analyze the structure of reovirus sigma-1 protein fibers. Not only is the structure regular but electron micrographs exist to compare predicted structure with image analysis after correlation alignment and correlation averaging. Correlation of predicted sequences with real structure (observed from image processing of electron micrographs) can yield greater understanding of protein structure and function.

As new sequences of regular (helical) proteins become available, it will be relatively easy to model these sequences and describe their structures both graphically and quantitatively.

Viral and Bacterial Structure As Determined by Image Processing of Electron Micrographs

B.L. Trus, Ph.D.

with: A.C. Steven, Ph.D. (NIAMS/LPB); M. Unser, Ph.D. (DRS/BEIB); M. Kessel (NIAMS/LPB).

Software is being developed (with NIAMS and BEIB) to analyze viral and bacterial images and perform various statistical and mathematical tests. Such images are typically analyzed by Fourier filtering techniques and the use of correlation alignment together with correlation averaging.

The electron micrographs are taken with a Philips EM400T microscope and the Brookhaven STEM. Some micrographs are preselected by optical diffraction. Negatives are digitized on a Perkin-Elmer 1010MG microdensitometer and analyzed by means of the PIC computer system. Results are photowritten on the Perkin-Elmer microdensitometer and on a Matrix camera station. Image processing uses software developed primarily at NIH.

The structure of the cell wall of Bordetella Pertussis is being studied in order to better understand the structure and functioning of this cell surface. The surface is composed of a two-dimensional lattice of a 40kDa protein porin.

Viruses are significantly smaller than bacteria, and as a result are not seen under a light microscope. Information about their structure comes from electron microscopy, which is limited by resolution, low contrast and noise. If stain is used, the resolution is limited by the size of the stain and often noise results from uneven staining. However, because virus structures are generally periodic or contain some symmetry, they are perfect candidates for image processing. This project should be considered as basic research aimed at increasing understanding of the structure and functions of viruses and bacteria in general, as well as of subclasses of viruses similar to those studied to date.

We anticipate evaluating other viruses and bacteria for examination suitability with these methods, and continuing this ongoing project to determine the structure of various classes of viruses.

Cataract Quantitation Using Image Processing

B.L. Trus, Ph.D.

with: M. Datiles, M.D., P. Edwards, M.D. (NEI/CB), K. Kashima, M.D. (NEI/CB), M. Unser, Ph.D. (BEIB/DRS).

Images produced by the Scheimpflug principle are being used to measure eye opacities in a study to evaluate the potential for the accurate evaluation of changes in cataract patients. This may provide a means of documenting and monitoring cataracts in vivo, allowing clinical trials of drugs that may prevent or reverse cataract formation.

Statistical evaluation of results is currently underway. In addition, computers are being used for classifying and clustering methodology for automatic identification or diagnosis of cataracts. A statistical study is determining the number of views necessary to characterize different types of cataracts. A group of normal controls is being used to study the effects of aging on the lens and how opacity increases with age.

Pharmaceuticals are available that may prevent or reverse cataract formation. A clinical trial in human patients cannot be pursued because of inadequate means of documenting and monitoring cataracts in vivo. It is hoped that this method will provide the statistical and image processing foundation to document and assess changes in lens opacities in cataract patients.

In classification studies the distance of a known or unknown from the normal class could indicate quantitatively how typical a normal lens is, or the degree of cataractous change. This method could be used in epidemiological studies, as well as clinical trials, and could provide a basis for diagnosis. In another experiment, we are attempting to determine the minimum number of views necessary to characterize different types of cataracts. The Scheimpflug camera can be used to take up to 18 images 10 degrees apart. While two perpendicular views can be used to evaluate some types of symmetrical (isotopic) cataracts, other asymmetric cataracts require six or nine views.

Nuclear Medicine Computer System

H. Ostrow

with: S. Bacharach, Ph.D., M. Green, M. Feldman (CC/NM); D. Vincent (DCRT/DMB).

CSL has continued to support the Nuclear Medicine Department by assessing their data processing needs and recommending appropriate solutions. This year Nuclear Medicine has continued its rapid rate of growth with respect to utilizing the equipment purchases over the past few years. As a result, the computer processing requirements continue to grow as anticipated.

Two years ago a department-wide computer system was installed. The system consists of a host (VAX8600 system) with 20 megabytes main memory and 3.0 gigabytes of disk storage along with six data acquisition systems (DAS), which are connected to the host via a local area network (LAN). This year additional DAS's were installed. The system is being used on a routine basis for image acquisition, storage and display.

We continued to work closely with Nuclear Medicine to develop an integrated system that will allow central storage of all the multimodality data, along with the retrieval and display of data and images from any location in the department. Last year we installed an additional network along with network software, and this year we upgraded the software to allow users with PC's transparent access to system capabilities. We are evaluating methods for distributing images around the department and working with DCRT's Data Management Branch to specify database requirements for Nuclear Medicine's unique research requirements.

Computer Support for Flow Cytometry/Electronic Cell Sorting (FC/ECS)

L.K. Barden

with: W. Gandler (DCRT/CSL).

The FC/ECS project provides consultation to NIH investigators at research oriented flow cytometry facilities in the areas of computer-based data acquisition, management and analysis.

This fiscal year, the Biological Resources Branch, NIAID flow cytometry facility has expanded to include five research grade cytometers, each with its own dedicated data acquisition and analysis system. Work is underway to provide a network connection for high-speed data file transfer among the major data systems within the facility.

During the year we have provided specialized maintenance and consultation on data system enhancements and upgrades to other facilities at NIH and at associated government facilities.

A flow cytometrist's guide to the use of logarithmic amplifiers was written and has been submitted to *Cytometry,* the journal of the Society for Analytical Cytology.

A major effort in FY89 will involve the BRB, NIAID facility, where we will proceed with the integration of the existing data acquisition, analysis and archiving subsystems and with upgrades to data acquisition and analysis software.

At the Experimental Immunology Branch, Division of Cancer Biology and Diagnosis, NCI site, an upgrade is being considered to the data acquisition system to bring this site in line with more standard systems on campus and plans are being made for the installation of a MicroVAX-II processor as part of the Flow Cytometry Advanced Data Analysis project.

Medical Information Technology Project

S.I. Allen, M.D.

with: C.S. Brown, M.D. (Bethesda).

This project's goal is to develop better ways to let physicians and their associates use computers in health care recordkeeping for research and patient care. The methodology focuses on providing disease-specific and problem-specific protocols and hierarchies of information that allow rapid convergence on relevant diagnoses, treatments, tests and procedures.

In past years, computer programs were developed for the physician to produce pharmacy prescriptions and drug-related patient information using high-speed menu selection methods. Later, new modules to aid in producing diagnostic schedules and treatment reports were developed. All these programs run on a personal computer (PC), and several PC's may be linked together in a local area network for clinics or practices needing more than one workstation.

Pilot studies with a dermatologist (C.S. Brown) involve the direct entry of medical transactions into a computer terminal by the physicians and staff during the doctor-patient encounter. Initial results with the PC system show more precise and more rapid prescription-writing.

Current work includes maintaining the demonstration programs for continuing research on doctor-computer interfacing; updating the medical databases, as required, with new concepts and products; restructuring medical data files for independent use in a modern database system; and exploring a technology transfer agreement with interested parties in the private sector.

Brain Image Registration

K.M. Kempner

with: M.V. Green, S.D. Stein (CC/NM); T.E. Nordahl, M.D., Ph.D. (NIMH/LCM), D.E. Rio, Ph.D. (NIAAA/LCS); J.J. Vucich (CC/DR); J.F. Fessler (DRS/BEIB).

An elusive problem faces researchers involved in the correlation of brain form (structure) from x-ray computed tomography (CT) images and brain function (metabolism) from nuclear medicine positron emission tomography (PET) images. The difficulty concerns the superposition and registration of the tomographic view obtained from these two imaging modalities.

The approach to this problem is based on a two-stage solution. First, practical methods for the accurate and reproducible placement of the head within a tomographic scanner's aperture are being developed. Second, simplified algorithms for the scaling and registration of digitized images from different scanners on a digital display subsystem are being developed.

Precise orientation of the subject's skull within the scanner's aperture is monitored and recorded through the use of a Polhemus Navigation Systems position/orientation transduction subsystem connected to an IBM PC/XT. Image processing and display will be performed utilizing the NIAAA imaging system, consisting of a DEC PDP-11/24 minicomputer and a Gould-DeAnza 6400 Image Processor subsystem.

Experimentation with sensor attachment techniques has resulted in the development of two inexpensive custom-molded oral appliances to allow the position/orientation subsystem's sensor to be fixed to the subject's skull. A solution to the head immobilization problem has been developed by project team members from the Nuclear Medicine Department using a moldable thermoplastic face mask. The position/orientation transduction subsystem has been used to evaluate the reduction in translational and rotational motions achieved with this head restraint system in normal volunteers and schizophrenic patients.

The importance of brain image registration is the need to develop a greater understanding of the processes underlying the generation of PET images. It is hoped that development of techniques for the accurate correlation of CT structural data with PET metabolic information will enhance this understanding.

Future efforts will center on evaluation and modification of targeting software. This software will provide the technician using the system with visual cues necessary for precise and reproducible head placement during sequential scans performed days or weeks apart.

Californium-252 Plasma Desorption Mass Spectrometer Data System

W. Gandler

with: L. Pannell, M.D. (NIDDK/LAC); A. Schultz (DCRT/CSL).

The Laboratory of Chemistry, NHLBI, has made productive use of the Californium-252 Plasma Desorption Mass Spectrometer since it was put into service in 1984. A new multistop time to digital converter (TDC) whose 30 nsec. internal dead time improves upon the current 850 nsec dead time was received from Institut de Physique Nucleaire-Orsay, France. CSL designed an interface between the new TDC and the Perkin-Elmer data bus that will enable high-speed data transfers in the existing format and use the existing software for data acquisition and analysis with minimal changes. The interface was designed to be synchronous for each stop time data transfer and is clocked by a 12 megahertz crystal. In addition, this project has involved dealing with the French developers of the TDC on problems related to reading out its data memory and identifying problems with the Perkin-Elmer data channel that required correction. The new TDC can now transfer data to the Perkin-Elmer computer, but a sporadic hardware problem with one of the 18 data bits must be corrected.

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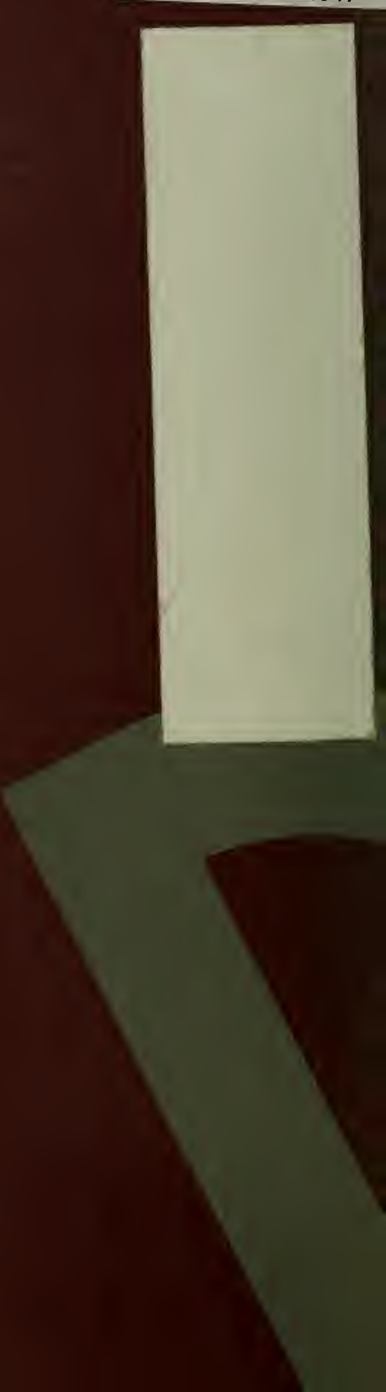

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